Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of *BRCA1* and *BRCA2* pathogenic variants

Daniel R. Barnes PhD[1]*, Matti A. Rookus PhD[2], Lesley McGuffog[1], Goska Leslie MEng[1], Thea M. Mooij MSc[2], Joe Dennis MSc[1], Nasim Mavaddat PhD[1], Julian Adlard MD[3], Munaza Ahmed MD(Res), FRCP[4], Kristiina Aittomäki MD, PhD[5], Nadine Andrieu PhD[6-9], Irene L. Andrulis PhD[10,11], Norbert Arnold PhD[12,13], Banu K. Arun MD[14], Jacopo Azzollini MD[15], Judith Balmaña MD, PhD[16,17], Rosa B. Barkardottir CandSci[18,19], Daniel Barrowdale BSc[1], Javier Benitez PhD[20,21], Pascaline Berthet MD[22], Katarzyna Białkowska MSc[23], Amie M. Blanco MS[24], Marinus J. Blok PhD[25], Bernardo Bonanni MD[26], Susanne E. Boonen MD, PhD[27], Åke Borg PhD[28], Aniko Bozsik PhD[29], Angela R. Bradbury MD[30], Paul Brennan MBBS, FRCP[31], Carole Brewer MD[32], Joan Brunet MD, PhD[33], Saundra S. Buys MD[34], Trinidad Caldés MD[35], Maria A. Caligo PhD[36], Ian Campbell PhD[37,38], Lise Lotte Christensen MSc, PhD[39], Wendy K. Chung MD, PhD[40], Kathleen B.M. Claes PhD[41], Chrystelle Colas MD, PhD[42], GEMO Study Collaborators [6-9], EMBRACE Collaborators [1], Marie-Agnès Collonge-Rame MD[43], Jackie Cook MD[44], Mary B. Daly MD, PhD[45], Rosemarie Davidson MD[46], Miguel de la Hoya PhD[35], Robin de Putter MD[41], Capucine Delnatte MD[47], Peter Devilee PhD[48,49], Orland Diez PhD[50,51], Yuan Chun Ding PhD[52], Susan M. Domchek MD[53], Cecilia M. Dorfling MSc[54], Martine Dumont PhD[55], Ros Eeles MD, PhD[56], Bent Ejlertsen MD[57], Christoph Engel MD[58], D. Gareth Evans MD, PhD[59,60], Laurence Faivre MD, PhD[61,62], Lenka Foretova MD, PhD[63], Florentia Fostira PhD[64], Michael Friedlander MD, PhD[65], Eitan Friedman MD, PhD[66,67], Debra Frost ONC[1], Patricia A. Ganz MD[68], Judy Garber MD MPH[69], Andrea Gehrig MD[70], Anne-Marie Gerdes MD[71], Paul Gesta MD[72], Sophie Giraud MD, PhD[73], Gord Glendon MSc[10], Andrew K. Godwin PhD[74], David E. Goldgar PhD[75], Anna González-Neira PhD[21], Mark H. Greene MD[76], Daphne Gschwantler-Kaulich MD[77], Eric Hahnen PhD[78,79], Ute Hamann PhD[80], Helen Hanson MD, FRCP[81], Julia Hentschel PhD[82], Frans B.L. Hogervorst PhD[83], Maartje J. Hooning PhD[84], Judit Horvath MD, PhD[85], Chunling Hu MD, PhD[86], Peter

J. Hulick MD[87,88], Evgeny N. Imyanitov MD[89], kConFab Investigators [37,38], HEBON Investigators [90], GENEPSO Investigators [91], Claudine Isaacs MD[92], Louise Izatt PhD[93], Angel Izquierdo MD, MPH[33], Anna Jakubowska PhD[23,94], Paul A. James MBBS, PhD[38,95], Ramunas Janavicius MD, PhD[96,97], Esther M. John PhD[98], Vijai Joseph PhD[99], Beth Y. Karlan MD[100,101], Karin Kast MD[102], Marco Koudijs PhD[103], Torben A. Kruse PhD[104], Ava Kwong MD[105-107], Yael Laitman MD[66], Christine Lasset MD, PhD[108,109], Conxi Lazaro PhD[33], Jenny Lester MPH[100,101], Fabienne Lesueur PhD[6-9], Annelie Liljegren MD, PhD[110], Jennifer T. Loud DNP, CRNP[76], Jan Lubiński MD, PhD[23], Phuong L. Mai MD, MS[111], Siranoush Manoukian MD[15], Véronique Mari MD[112], Noura Mebirouk PhD[6-9], Hanne E.J. Meijers-Heijboer PhD[113], Alfons Meindl PhD[114], Arjen R. Mensenkamp PhD[115], Austin Miller PhD[116], Marco Montagna PhD[117], Emmanuelle Mouret-Fourme MD[42], Semanti Mukherjee PhD[118], Anna Marie Mulligan MBBCh[119,120], Katherine L. Nathanson PhD[53], Susan L. Neuhausen PhD[52], Heli Nevanlinna PhD[121], Dieter Niederacher PhD[122], Finn Cilius Nielsen MD[123], Liene Nikitina-Zake MD, PhD[124], Catherine Noguès MD[91], Edith Olah PhD, DSc[29], Olufunmilayo I. Olopade MD[125], Kai-ren Ong MD[126], Aoife O'Shaughnessy-Kirwan PhD[127], Ana Osorio PhD[20,21], Claus-Eric Ott MD[128], Laura Papi MD, PhD[129], Sue K. Park MD, PhD[130-132], Michael T. Parsons PhD[133], Inge Sokilde Pedersen PhD[134-136], Bernard Peissel MD[15], Ana Peixoto MSc[137], Paolo Peterlongo PhD[138], Georg Pfeiler MD[139], Kelly-Anne Phillips MD[37,38,140,141], Karolina Prajzendanc MSc[23], Miquel Angel Pujana PhD[142], Paolo Radice PhD[143], Juliane Ramser PhD[144], Susan J. Ramus PhD[145-147], Johanna Rantala PhD[148], Gad Rennert MD, PhD[149], Harvey A. Risch MD, PhD[150], Mark Robson MD[118], Karina Rønlund MD, PhD[151], Ritu Salani MD, MBA[152], Hélène Schuster MD[153-155], Leigha Senter MS[156], Payal D. Shah MD[30], Priyanka Sharma MD[157], Lucy E. Side MD[158], Christian F. Singer MD, MPH[139], Thomas P. Slavin MD[159], Penny Soucy PhD[55], Melissa C. Southey PhD[160-162], Amanda B. Spurdle PhD[133], Doris Steinemann PhD[163], Zoe Steinsnyder BS[118], Dominique Stoppa-Lyonnet MD, PhD[42,164,165], Christian Sutter PhD[166], Yen Yen Tan PhD[77], Manuel R. Teixeira MD, PhD[137,167], Soo Hwang Teo PhD[168,169], Darcy L. Thull MS[170], Marc Tischkowitz MD, PhD[171,172], Silvia Tognazzo MSc[117], Amanda E. Toland PhD[173], Alison H. Trainer MBBS,

PhD[95,174], Nadine Tung MD[175], Klaartje van Engelen MD[176], Elizabeth J. van Rensburg PhD[54], Ana Vega PhD[177-179], Jeroen Vierstraete MSc[41], Gabriel Wagner MSc[139], Lisa Walker PhD[180], Shan Wang-Gohrke MD, PhD[181], Barbara Wappenschmidt MD[78,79], Jeffrey N. Weitzel MD[159], Siddhartha Yadav MBBS[182], Xin Yang PhD[1], Drakoulis Yannoukakos PhD[64], Dario Zimbalatti MD[15], Kenneth Offit MD, MPH[99,118], Mads Thomassen PhD[104], Fergus J. Couch PhD[86], Rita K. Schmutzler MD[78,79,183], Jacques Simard PhD[55], Douglas F. Easton PhD[1,184], Georgia Chenevix-Trench PhD[133], Antonis C. Antoniou PhD[1] on behalf of the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2*

[1] Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

[2] The Netherlands Cancer Institute, Department of Epidemiology (PSOE), Amsterdam, The Netherlands.

[3] Chapel Allerton Hospital, Yorkshire Regional Genetics Service, Leeds, UK.

[4] Great Ormond Street Hospital for Children NHS Trust, North East Thames Regional Genetics Service, London, UK.

[5] University of Helsinki, Department of Clinical Genetics, Helsinki University Hospital, Helsinki, Finland.

[6] Inserm U900, Genetic Epidemiology of Cancer team, Paris, France.

[7] Institut Curie, Paris, France.

[8] Mines ParisTech, Fontainebleau, France.

[9] PSL University, Paris, France.

[10] Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Fred A. Litwin Center for Cancer Genetics, Toronto, ON, Canada.

[11] University of Toronto, Department of Molecular Genetics, Toronto, ON, Canada.

[12] University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Department of Gynaecology and Obstetrics, Kiel, Germany.

[13] University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University

Kiel, Institute of Clinical Molecular Biology, Kiel, Germany.

[14] University of Texas MD Anderson Cancer Center, Department of Breast Medical Oncology, Houston, TX, USA.

[15] Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Unit of Medical Genetics, Department of Medical Oncology and Hematology, Milan, Italy.

[16] Vall d'Hebron Institute of Oncology, High Risk and Cancer Prevention Group, Barcelona, Spain.

[17] University Hospital of Vall d'Hebron, Department of Medical Oncology, Barcelona, Spain.

[18] Landspitali University Hospital, Department of Pathology, Reykjavik, Iceland.

[19] University of Iceland, BMC (Biomedical Centre), Faculty of Medicine, Reykjavik, Iceland.

[20] Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain.

[21] Spanish National Cancer Research Centre (CNIO), Human Cancer Genetics Programme, Madrid, Spain.

[22] Centre François Baclesse, Département de Biopathologie, Caen, France.

[23] Pomeranian Medical University, Department of Genetics and Pathology, Szczecin, Poland.

[24] University of California San Francisco, Cancer Genetics and Prevention Program, San Francisco, CA, USA.

[25] Maastricht University Medical Center, Department of Clinical Genetics, Maastricht, The Netherlands.

[26] IEO, European Institute of Oncology IRCCS, Division of Cancer Prevention and Genetics, Milan, Italy.

[27] Zealand University Hospital, Clinical Genetic Unit, Department of Paediatrics, Roskilde, Denmark.

[28] Lund University, Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund, Sweden.

[29] National Institute of Oncology, Department of Molecular Genetics, Budapest, Hungary.

[30] Perelman School of Medicine at the University of Pennsylvania, Department of Medicine,

Abramson Cancer Center, Philadelphia, PA, USA.

[31] Institute of Genetic Medicine, International Centre for Life, Northern Genetic Service, Newcastle upon Tyne, UK.

[32] Royal Devon & Exeter Hospital, Department of Clinical Genetics, Exeter, UK.

[33] ONCOBELL-IDIBELL-IDIBGI-IGTP, Catalan Institute of Oncology, CIBERONC, Hereditary Cancer Program, Barcelona, Spain.

[34] Huntsman Cancer Institute, Department of Medicine, Salt Lake City, UT, USA.

[35] CIBERONC, Hospital Clinico San Carlos, IdISSC (Instituto de Investigación Sanitaria del Hospital Clínico San Carlos), Molecular Oncology Laboratory, Madrid, Spain.

[36] University Hospital, SOD Genetica Molecolare, Pisa, Italy.

[37] Peter MacCallum Cancer Center, Melbourne, Victoria, Australia.

[38] The University of Melbourne, Sir Peter MacCallum Department of Oncology, Melbourne, Victoria, Australia.

[39] Aarhus University Hospital, Department of Clinical Medicine, Aarhus N, Denmark.

[40] Columbia University, Departments of Pediatrics and Medicine, New York, NY, USA.

[41] Ghent University, Centre for Medical Genetics, Gent, Belgium.

[42] Institut Curie, Service de Génétique, Paris, France.

[43] CHU de Besançon, Service de Génétique, Besançon, France.

[44] Sheffield Children's Hospital, Sheffield Clinical Genetics Service, Sheffield, UK.

[45] Fox Chase Cancer Center, Department of Clinical Genetics, Philadelphia, PA, USA.

[46] Queen Elizabeth University Hospitals, Department of Clinical Genetics, Glasgow, UK.

[47] CHU Nantes, Laboratoire de genetique moleculaire, Nantes, France.

[48] Leiden University Medical Center, Department of Pathology, Leiden, The Netherlands.

[49] Leiden University Medical Center, Department of Human Genetics, Leiden, The Netherlands.

[50] Vall dHebron Institute of Oncology (VHIO), Oncogenetics Group, Barcelona, Spain.

[51] University Hospital Vall dHebron, Clinical and Molecular Genetics Area, Barcelona, Spain.

[52] Beckman Research Institute of City of Hope, Department of Population Sciences, Duarte,

CA, USA.

[53] University of Pennsylvania, Basser Center for BRCA, Abramson Cancer Center, Philadelphia, PA, USA.

[54] University of Pretoria, Department of Genetics, Arcadia, South Africa.

[55] Centre Hospitalier Universitaire de Québec – Université Laval Research Center, Genomics Center, Québec City, QC, Canada.

[56] The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Oncogenetics Team, London, UK.

[57] Rigshospitalet, Copenhagen University Hospital, Department of Oncology, Copenhagen, Denmark.

[58] University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany.

[59] The University of Manchester, Manchester Academic Health Science Centre, Manchester Universities Foundation Trust, St. Mary's Hospital, Genomic Medicine, Division of Evolution and Genomic Sciences, Manchester, UK.

[60] Manchester Academic Health Science Centre, Manchester Universities Foundation Trust, St. Mary's Hospital, Genomic Medicine, North West Genomics hub, Manchester, UK.

[61] Centre Georges-François Leclerc, Unité d'oncogénétique, Centre de Lutte Contre le Cancer, Dijon, France.

[62] DHU Dijon, Centre de Génétique, Dijon, France.

[63] Masaryk Memorial Cancer Institute, Department of Cancer Epidemiology and Genetics, Brno, Czech Republic.

[64] National Centre for Scientific Research 'Demokritos', Molecular Diagnostics Laboratory, INRASTES, Athens, Greece.

[65] NHMRC Clinical Trials, ANZ GOTG Coordinating Centre, Camperdown, NSW, Australia.

[66] Chaim Sheba Medical Center, The Susanne Levy Gertner Oncogenetics Unit, Ramat Gan, Israel.

[67] Tel Aviv University, Sackler Faculty of Medicine, Ramat Aviv, Israel.

[68] Jonsson Comprehensive Cancer Centre, UCLA, Schools of Medicine and Public Health, Division of Cancer Prevention & Control Research, Los Angeles, CA, USA.

[69] Dana-Farber Cancer Institute, Cancer Risk and Prevention Clinic, Boston, MA, USA.

[70] University Würzburg, Department of Human Genetics, Würzburg, Germany.

[71] Rigshospitalet, Copenhagen University Hospital, Department of Clinical Genetics, Copenhagen, Denmark.

[72] CH Niort, Service Régional Oncogénétique Poitou-Charentes, Niort, France.

[73] Hospices Civils de Lyon, Department of Genetics, Bron, France.

[74] University of Kansas Medical Center, Department of Pathology and Laboratory Medicine, Kansas City, KS, USA.

[75] Huntsman Cancer Institute, University of Utah School of Medicine, Department of Dermatology, Salt Lake City, UT, USA.

[76] Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA.

[77] Medical University of Vienna, Dept of OB/GYN, Vienna, Austria.

[78] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Familial Breast and Ovarian Cancer, Cologne, Germany.

[79] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Integrated Oncology (CIO), Cologne, Germany.

[80] German Cancer Research Center (DKFZ), Molecular Genetics of Breast Cancer, Heidelberg, Germany.

[81] St George's NHS Foundation Trust, Southwest Thames Regional Genetics Service, London, UK.

[82] University Hospital Leipzig, Institute of Human Genetics, Leipzig, Germany.

[83] The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Family Cancer Clinic, Amsterdam, The Netherlands.

[84] Erasmus MC Cancer Institute, Department of Medical Oncology, Family Cancer Clinic, Rotterdam, The Netherlands.

[85] University of Münster, Institute of Human Genetics, Münster, Germany.

[86] Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN, USA.

[87] NorthShore University HealthSystem, Center for Medical Genetics, Evanston, IL, USA.

[88] The University of Chicago Pritzker School of Medicine, Chicago, IL, USA.

[89] N.N. Petrov Institute of Oncology, St. Petersburg, Russia.

[90] Coordinating center: The Netherlands Cancer Institute, The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Amsterdam, The Netherlands.

[91] Oncogénétique Clinique and Aix Marseille Univ, INSERM, IRD, SESSTIM, Institut Paoli-Calmettes, Département d'Anticipation et de Suivi des Cancers, Marseille, France.

[92] Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA.

[93] Guy's and St Thomas' NHS Foundation Trust, Clinical Genetics, London, UK.

[94] Pomeranian Medical University, Independent Laboratory of Molecular Biology and Genetic Diagnostics, Szczecin, Poland.

[95] Peter MacCallum Cancer Center, Parkville Familial Cancer Centre, Melbourne, Victoria, Australia.

[96] Vilnius University Hospital Santariskiu Clinics, Hematology, oncology and transfusion medicine center, Dept. of Molecular and Regenerative Medicine, Vilnius, Lithuania.

[97] State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania.

[98] Stanford Cancer Institute, Stanford University School of Medicine, Department of Medicine, Division of Oncology, Stanford, CA, USA.

[99] Memorial Sloan-Kettering Cancer Center, Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, New York, NY, USA.

[100] University of California at Los Angeles, David Geffen School of Medicine, Department of Obstetrics and Gynecology, Los Angeles, CA, USA.

[101] Cedars-Sinai Medical Center, Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, USA.

[102] Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

[103] University Medical Center Utrecht, Department of Medical Genetics, Utrecht, The Netherlands.

[104] Odense University Hospital, Department of Clinical Genetics, Odence C, Denmark.

[105] Cancer Genetics Centre, Hong Kong Hereditary Breast Cancer Family Registry, Happy Valley, Hong Kong.

[106] The University of Hong Kong, Department of Surgery, Pok Fu Lam, Hong Kong.

[107] Hong Kong Sanatorium and Hospital, Department of Surgery, Happy Valley, Hong Kong.

[108] Centre Léon Bérard, Unité de Prévention et d'Epidémiologie Génétique, Lyon, France.

[109] Lyon University, UMR CNRS 5558, Lyon, France.

[110] Karolinska Institutet, Department of Oncology, Stockholm, Sweden.

[111] Magee-Womens Hospital, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

[112] Centre Antoine Lacassagne, Département d'Hématologie-Oncologie Médicale, Nice, France.

[113] Amsterdam UMC, location AMC, Department of Clinical Genetics, Amsterdam, The Netherlands.

[114] University of Munich, Campus Großhadern, Department of Gynecology and Obstetrics, Munich, Germany.

[115] Radboud University Medical Center, Department of Human Genetics, Nijmegen, The Netherlands.

[116] Roswell Park Cancer Institute, NRG Oncology, Statistics and Data Management Center, Buffalo, NY, USA.

[117] Veneto Institute of Oncology IOV - IRCCS, Immunology and Molecular Oncology Unit, Padua, Italy.

[118] Memorial Sloan-Kettering Cancer Center, Clinical Genetics Service, Department of Medicine, New York, NY, USA.

[119] University of Toronto, Department of Laboratory Medicine and Pathobiology, Toronto, ON, Canada.

[120] University Health Network, Laboratory Medicine Program, Toronto, ON, Canada.

[121] University of Helsinki, Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, Finland.

[122] University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf, Department of Gynecology and Obstetrics, Düsseldorf, Germany.

[123] Rigshospitalet, Copenhagen University Hospital, Center for Genomic Medicine, Copenhagen, Denmark.

[124] Latvian Biomedical Research and Study Centre, Riga, Latvia.

[125] The University of Chicago, Center for Clinical Cancer Genetics, Chicago, IL, USA.

[126] Birmingham Women's Hospital Healthcare NHS Trust, West Midlands Regional Genetics Service, Birmingham, UK.

[127] Cambridge University Hospitals NHS Foundation Trust, East Anglian Medical Genetics Service, Cambridge, UK.

[128] Campus Virchov Klinikum, Charite, Institute of Human Genetics, Berlin, Germany.

[129] University of Florence, Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', Medical Genetics Unit, Florence, Italy.

[130] Seoul National University College of Medicine, Department of Preventive Medicine, Seoul, Korea.

[131] Seoul National University Graduate School, Department of Biomedical Sciences, Seoul, Korea.

[132] Seoul National University, Cancer Research Institute, Seoul, Korea.

[133] QIMR Berghofer Medical Research Institute, Department of Genetics and Computational Biology, Brisbane, Queensland, Australia.

[134] Aalborg University Hospital, Molecular Diagnostics, Aalborg, Denmark.

[135] Aalborg University Hospital, Clinical Cancer Research Center, Aalborg, Denmark.

[136] Aalborg University, Department of Clinical Medicine, Aalborg, Denmark.

[137] Portuguese Oncology Institute, Department of Genetics, Porto, Portugal.

[138] IFOM - the FIRC Institute of Molecular Oncology, Genome Diagnostics Program, Milan,

Italy.

[139] Medical University of Vienna, Dept of OB/GYN and Comprehensive Cancer Center, Vienna, Austria.

[140] The University of Melbourne, Department of Medicine, St Vincent's Hospital, Fitzroy, Victoria, Australia.

[141] The University of Melbourne, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Melbourne, Victoria, Australia.

[142] IDIBELL (Bellvitge Biomedical Research Institute), Catalan Institute of Oncology, ProCURE, Barcelona, Spain.

[143] Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Milan, Italy.

[144] Klinikum rechts der Isar der Technischen Universität München, Department of Gynaecology and Obstetrics, Munich, Germany.

[145] University of NSW Sydney, School of Women's and Children's Health, Faculty of Medicine, Sydney, New South Wales, Australia.

[146] The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, New South Wales, Australia.

[147] University of NSW Sydney, Adult Cancer Program, Lowy Cancer Research Centre, Sydney, New South Wales, Australia.

[148] Karolinska Institutet, Clinical Genetics, Stockholm, Sweden.

[149] Carmel Medical Center and Technion Faculty of Medicine, Clalit National Cancer Control Center, Haifa, Israel.

[150] Yale School of Medicine, Chronic Disease Epidemiology, New Haven, CT, USA.

[151] Region of Southern Denmark, Vejle Hospital, Department of Clinical Genetics, Denmark.

[152] Wexner Medical Center, The Ohio State University, Department of Gynecology and Obstetrics, Columbus, OH, USA.

[153] Unité d'Oncogénétique Centre de Lutte contre le Cancer Paul Strauss, Strasbourg, France.

[154] Institut de Cancérologie Strasbourg Europe, ICANS, Strasbourg, France.

[155] Université de Strasbourg, Laboratoire d'ImmunoRhumatologie Moléculaire, Plateforme GENOMAX, INSERM UMR_S 1109, LabEx TRANSPLANTEX, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Faculté de Médecine, Strasbourg, France.

[156] The Ohio State University, Clinical Cancer Genetics Program, Division of Human Genetics, Department of Internal Medicine, The Comprehensive Cancer Center, Columbus, OH, USA.

[157] University of Kansas Medical Center, Department of Internal Medicine, Division of Medical Oncology, Westwood, KS, USA.

[158] Princess Anne Hospital, Southampton, UK.

[159] City of Hope, Clinical Cancer Genomics, Duarte, CA, USA.

[160] Monash University, Precision Medicine, School of Clinical Sciences at Monash Health, Clayton, Victoria, Australia.

[161] The University of Melbourne, Department of Clinical Pathology, Melbourne, Victoria, Australia.

[162] Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Victoria, Australia.

[163] Hannover Medical School, Institute of Human Genetics, Hannover, Germany.

[164] INSERM U830, Department of Tumour Biology, Paris, France.

[165] Université Paris Descartes, Paris, France.

[166] University Hospital Heidelberg, Institute of Human Genetics, Heidelberg, Germany.

[167] University of Porto, Biomedical Sciences Institute (ICBAS), Porto, Portugal.

[168] Cancer Research Malaysia, Breast Cancer Research Programme, Subang Jaya, Selangor, Malaysia.

[169] University of Malaya, Department of Surgery, Faculty of Medicine, Kuala Lumpur, Malaysia.

[170] Magee-Womens Hospital, University of Pittsburgh School of Medicine, Department of Medicine, Pittsburgh, PA, USA.

[171] McGill University, Program in Cancer Genetics, Departments of Human Genetics and

Oncology, Montréal, QC, Canada.

[172] University of Cambridge, Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, UK.

[173] The Ohio State University, Department of Cancer Biology and Genetics, Columbus, OH, USA.

[174] University Of Melbourne, Department of medicine, Melbourne, Victoria, Australia.

[175] Beth Israel Deaconess Medical Center, Department of Medical Oncology, Boston, MA, USA.

[176] Amsterdam UMC, location VUmc, Department of Clinical Genetics, Amsterdam, The Netherlands.

[177] Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain.

[178] Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain.

[179] Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain.

[180] Oxford University Hospitals, Oxford Centre for Genomic Medicine, Oxford, UK.

[181] University Hospital Ulm, Department of Gynaecology and Obstetrics, Ulm, Germany.

[182] Mayo Clinic, Department of Oncology, Rochester, MN, USA.

[183] Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany.

[184] Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK.

* Corresponding author:

Dr Daniel R Barnes

Centre for Cancer Genetic Epidemiology, Strangeways Research Laboratory,

2 Worts Causeway, Cambridge, CB1 8RN, UK

+44 (0) 1223 748641

drb54@medschl.cam.ac.uk

CONFLICT OF INTEREST DISCLOSURES

Prof. Georg Pfeiler has received honoraria from Novartis, Amgen, Roche, Pfizer and AstraZeneca.

ABSTRACT

Purpose: We assessed the associations between population-based polygenic risk scores (PRS) for breast (BC) or epithelial ovarian cancer (EOC) with cancer risks for *BRCA1* and *BRCA2* pathogenic variant carriers.

Methods: Retrospective cohort data on 18,935 *BRCA1* and 12,339 *BRCA2* female pathogenic variant carriers of European ancestry were available. Three versions of a 313-SNP BC PRS were evaluated based on whether it predicts overall, estrogen-receptor (ER)-negative or ER-positive BC; and two PRS for overall or high-grade serous EOC. Associations were validated in a prospective cohort.

Results: The ER-negative PRS showed the strongest association with BC risk for *BRCA1* carriers (Hazard Ratio (HR) per standard deviation=1.29 (95%CI 1.25-1.33), $P=3x10^{-72}$). For *BRCA2,* the strongest association was with overall BC PRS (HR=1.31 (95%CI 1.27-1.36), $P=7x10^{-50}$). HR estimates decreased significantly with age and there was evidence for differences in associations by predicted variant-effects on protein expression. The HR estimates were smaller than general population estimates. The high-grade serous PRS yielded the strongest associations with EOC risk for *BRCA1* (HR=1.32 (95%CI 1.25-1.40), $P=3x10^{-22}$) and *BRCA2* (HR=1.44 (95%CI 1.30-1.60), $P=4x10^{-12}$) carriers. The associations in the prospective cohort were similar.

Conclusion: Population-based PRS are strongly associated with BC and EOC risks for *BRCA1*/*2* carriers and predict substantial absolute risk differences for women at PRS distribution extremes.

Key words: *BRCA1*/*2*, breast cancer, ovarian cancer, PRS, genetics

INTRODUCTION

Pathogenic variants in *BRCA1* and *BRCA2* are associated with high risk of developing breast and ovarian cancers[1,2]. A recent study of *BRCA1*/*2* carriers estimated the average risk of developing breast cancer by age 80-years to be 72% for *BRCA1* and 69% for *BRCA2* carriers[2]. Corresponding ovarian cancer risks were 44% for *BRCA1* and 17% for *BRCA2* carriers. This and previous studies have demonstrated that cancer risks for *BRCA1*/*2* carriers increase with an increasing number of affected first- or second-degree relatives[2], suggesting genetic or other familial factors modify cancer risks for *BRCA1*/*2* carriers. Consistent with this observation, common breast and ovarian cancer susceptibility single nucleotide polymorphisms (SNPs), identified through genome-wide association studies (GWAS) in the general population, have been shown to modify breast and ovarian cancer risks for *BRCA1*/*2* carriers[3-7].

Polygenic risk scores (PRS) based on the combined effects of disease-associated SNPs, can lead to significant levels of breast and ovarian cancer risk-stratification in the general population[8,9]. It has also been demonstrated that PRS can result in large absolute risk differences of developing these cancers for *BRCA1*/*2* carriers[10]. The largest study to date was a retrospective cohort study of 23,463 carriers using a PRS based on up to 88 breast cancer susceptibility SNPs and a PRS based on up to 17 ovarian cancer susceptibility SNPs[10].

Recent population-based GWAS identified an additional 72 breast and 12 ovarian cancer susceptibility SNPs[6,7,11]. Based on these data, PRS have been constructed that include SNPs associated at both genome-wide and sub-genome-wide significance levels. The best performing PRS for breast cancer includes 313 SNPs[12].

It is therefore important to understand how the most recently developed breast and ovarian cancer PRS modify cancer risks for *BRCA1*/*2* carriers, as this information will be necessary for implementation studies to evaluate how their application influences cancer risk management for women with pathogenic variants in these genes. In this study, we used the

largest sample of women with pathogenic *BRCA1*/*2* variants currently available to assess the associations between the most recently developed PRS with cancer risks for *BRCA1*/*2* carriers. We evaluated how these PRS associations vary with age, cancer family history, and *BRCA1*/*2* gene-variant characteristics. We further validated the associations for the first time in a prospective cohort of carriers and investigated implications for cancer risk prediction.

PARTICIPANTS AND METHODS

Retrospective cohort study participants

Study participants were enrolled through 63 studies from 29 countries contributing to the Consortium of Investigators of Modifiers of *BRCA1*/*2* (CIMBA)[13]. Eligibility was restricted to women who were ≥18-years old at recruitment and carried a pathogenic *BRCA1*/*2* variant. CIMBA collected information on year of birth, variant description, age at study recruitment and last follow-up, age at breast and ovarian cancer (including invasive ovarian, fallopian tube, or peritoneal) diagnosis, age/date at bilateral prophylactic mastectomy, and number of first- and second-degree relatives with breast or ovarian cancer. Related individuals were tracked through a unique family identifier. The majority of study participants were recruited through cancer genetics clinics and enrolled in regional or national research studies. Variants were categorised according to their predicted or known effect on cellular protein expression: “class I” included loss-of-function pathogenic variants expected to result in unstable or no protein; “class II” included variants likely to yield stable mutant proteins[14]. Breast cancer pathology data were available from pathology reviews, tumour registry records, medical records or pathology records, and from tissue microarray immunohistochemical staining[15].

The genotyping, quality control and imputation processes have been described in detail previously[6,7] (brief description provided in supplement). The present study was restricted to carriers of *BRCA1*/*2* pathogenic variants of European ancestry, determined using genetic data and multidimensional scaling[6,7].

Breast cancer PRS

The methods for calculating the PRS are described in the supplementary material. We evaluated three versions of the published breast cancer PRS based on the same 313 SNPs, with different weights optimised to predict the risk of overall breast cancer (PRS_{BC}), ER-negative (PRS_{ER-}) or ER-positive (PRS_{ER+}) breast cancer[12] (Table S1).

The breast cancer PRS were standardised using the standard deviations (SDs) of the corresponding PRS in population-based controls. Therefore, the estimated hazard ratios (HRs) from this study are directly comparable to odds ratios (ORs) estimated from population-based data[12].

Epithelial ovarian cancer PRS

We constructed ovarian cancer PRS based on ovarian cancer susceptibility SNPs identified through GWAS[7]. Two ovarian cancer PRS were constructed: one for all invasive epithelial ovarian cancer (EOC) using 30 SNPs (PRS_{EOC}); and one for predicting high-grade serous (HGS) EOC using 22 SNPs (PRS_{HGS}) (supplementary material, Table S2). HGS is the predominant EOC-histotype in *BRCA1*/*2* tumours[16].

The PRS SDs in unaffected women in our sample were used to standardise PRS_{EOC} and PRS_{HGS}.

Associations between PRS and breast cancer risk

Associations between PRS and breast cancer risk for *BRCA1*/*2* carriers were assessed using the CIMBA retrospective cohort. Study participants were censored at the first of: (i) breast cancer diagnosis; (ii) ovarian cancer diagnosis; (iii) risk-reducing bilateral mastectomy; (iv) last follow-up; or (v) age 80-years. Participants with a first breast cancer diagnosis were considered affected. To account for non-random sampling with respect to disease status, associations were evaluated using weighted Cox regression[17,18]. This involved assigning age- and disease-specific sampling weights, such that observed weighted

age-specific incidences agreed with established incidences for *BRCA1*/*2* pathogenic variant carriers (supplementary material)[19].

We assessed the associations between three breast cancer PRS with the risk of overall breast cancer, and separately with ER-positive or ER-negative breast cancer risk. Models were stratified by country and Ashkenazi Jewish ancestry and were adjusted for birth cohort and the first four ancestry informative principal components calculated separately by genotyping array (supplementary material). We fitted models adjusting for family history of breast cancer in first- and second-degree relatives to determine whether cancer family history was a confounder of PRS associations. Family history was coded as no family history, or one relative, or two or more relatives diagnosed with breast cancer. Robust variances were calculated to account for the inclusion of related individuals by clustering on family membership. All models were fitted separately in *BRCA1* and *BRCA2* carriers.

We fitted separate models in which (i) the PRS was assumed to be continuous and (ii) categorical based on PRS percentiles determined by the PRS distribution in unaffected carriers. We tested for variation in the association of the PRS by age by fitting Cox-regression models in which the PRS was a time-varying covariate, with age as the time-scale, that included a PRS main effect and a PRS-by-age interaction term. Heterogeneity in the associations across countries was assessed by fitting models with a PRS-country interaction term. A likelihood ratio test (LRT) was used to assess statistical significance of interaction terms by comparing the models with the interaction against a model without the interaction term (supplementary material). Similarly, LRTs were used to compare the fit of nested models.

Previous studies have demonstrated that cancer risks for *BRCA1*/*2* carriers vary by pathogenic variant location or functional effect[2,20]. To investigate whether the PRS associations varied by *BRCA1/2*-variant location, we fitted models that included a PRS by location interaction. Variants were grouped into regions by nucleotide position on the basis of previously reported differences in breast or ovarian cancer risks. *BRCA1* variants were grouped in three regions (5' to c.2281, c.2282 to c.4071 and c.4072 to 3')[20,21]. The *BRCA2*

ovarian cancer cluster region (OCCR) was used to define the variant location groups[20,22]. Two *BRCA2* OCCR definitions were used: "narrow" (5' to c.3846, c.3847 to c.6275, c.6276 to 3') and "wide" (5' to c.2831, c.2832 to c.6401, c.6402 to 3'). We also investigated variation in PRS associations by the predicted variant effect on protein stability/expression ("class I" *versus* "class II", defined above).

To assess the associations with ER-specific breast cancer risk, a similar censoring process was used except the event of interest was diagnosis of either ER-positive or ER-negative breast cancer. Affected carriers with the alternative ER-status to the outcome of interest were censored at that diagnosis. Carriers with missing ER-status were excluded from the analysis.

Associations with epithelial ovarian cancer risk

The associations with EOC risk were evaluated following a similar process. However, women were censored at bilateral risk-reducing salpingo-oophorectomy (RRSO) rather than bilateral mastectomy. Carriers with a first ovarian cancer diagnosis were assumed to be affected in this analysis. We also fitted models that adjusted for family history of ovarian cancer in first- and second-degree relatives, coded as no family history, or one relative, or two or more relatives diagnosed with the disease.

The discriminatory ability of each PRS was assessed by Harrell's C-statistic[23] stratified by country and Ashkenazi Jewish ancestry and adjusted for birth cohort and principal components[24]. Standard errors were estimated using 1,000 bootstrap replications.

Validation in prospective cohorts

The PRS associations were further evaluated using prospective cohort data. The prospective cohort included pathogenic variant carriers from the *BRCA1* and *BRCA2* Cohort Consortium (BBCC)[2] and CIMBA[13] who were unaffected at recruitment (informed consent and baseline questionnaire). The BBCC included data from the International *BRCA1*/*2*

Carrier Cohort Study (IBCCS), Breast Cancer Family Registry (BCFR) and the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) (details in supplementary material)[2]. Only women of European ancestry were included in the analysis. All prospective cohort participants were genotyped as part of the CIMBA effort described above. However, prospective analyses considered only the prospective follow-up period from the time at recruitment of each participant into the study. Thus, the analysis time considered in the prospective and retrospective analyses were completely distinct. Associations were evaluated using Cox regression, separately for *BRCA1* and *BRCA2* carriers. The censoring process and analysis are described in detail in the supplementary materials.

Predicted age-specific cancer risks by PRS

Retrospective analysis HR estimates were used to predict age-specific absolute risks of developing breast and ovarian cancer by PRS percentiles following a previously published method[25]. To ensure consistency with known cancer risks for *BRCA1*/*2* carriers, average age-specific cancer incidences were constrained over PRS percentile categories to agree with external estimates of cancer incidences for carriers[2] (supplementary material). We also calculated absolute breast cancer risks for carriers in the absence or presence of cancer family history and by *BRCA2* variant location, assuming external average cancer incidences by family history and variant location[2]. The absolute risks were used to calculate 10-year cancer risks at each age by different PRS percentiles (supplementary material).

Ethics Statement

All study participants provided written informed consent and participated in research or clinical studies at the host institute under ethically approved protocols. The studies and their approving institutes are listed as a separate online Supplement.

All statistical tests were two-sided. Retrospective and prospective cohort analyses were

performed using R 3.5.1. Age-varying PRS and discrimination analyses were conducted using Stata 13.1 (supplementary material).

RESULTS

The CIMBA retrospective cohort consisted of 18,935 *BRCA1* carriers (9,473 diagnosed with breast and 2,068 with ovarian cancer) and 12,339 *BRCA2* carriers (6,332 with breast and 718 with ovarian cancer, Table S3).

The SNPs included in the PRSs were well imputed on both genotyping platforms (supplementary material, Figures S1 and S2, Tables S1 and S2). The average PRSs were larger for women diagnosed with cancer, compared with unaffected carriers (Table S3), but the PRS SDs were similar in unaffected and affected carriers (Table S3).

Associations with breast cancer risk

Table 1 shows the associations between PRS_{BC}, PRS_{ER-} and PRS_{ER+} and overall breast cancer risk for carriers using the CIMBA retrospective cohort data. PRS_{ER-} yielded the strongest association for *BRCA1* carriers (per SD HR=1.29, 95%CI=1.25-1.33, $P=3x10^{-72}$). For *BRCA2* carriers, the strongest associations were found for PRS_{BC} (per SD HR=1.31, 95%CI=1.27-1.36, $P=7x10^{-50}$) and PRS_{ER+} (per SD HR=1.31, 95%CI=1.26-1.36, $P=6x10^{-49}$). Adjusting for breast cancer family history yielded similar associations between the PRS and breast cancer risk to those observed in the unadjusted models (Table 1). Family history was significantly associated with risk in all models.

The PRS_{ER-} and PRS_{BC} were used for subsequent *BRCA1* and *BRCA2* carrier analyses, respectively. There was no statistically significant evidence of heterogeneity in the country-specific HR estimates (*BRCA1* $P_{LRT}=0.26$, *BRCA2* $P_{LRT}=0.64$; Figure S3). The estimated HRs for each PRS percentile category (Table 2) were consistent with the HRs predicted under models with the continuous PRS (estimated above), but were attenuated compared to the HRs expected under the population-based PRS distributions (Figures 1A

and 1B). Models estimating PRS percentile-specific associations did not fit significantly better than models in which PRS were continuous (*BRCA1* carriers P_{LRT}=0.18; *BRCA2* carriers P_{LRT}=0.99). The HRs for the breast cancer association decreased with age (Table 2; PRS-by-age interaction HRs: *BRCA1* HR=0.996, P=0.003; *BRCA2* HR=0.994, P=9.40x10^{-5}). The HRs for the PRS associations with breast cancer risk did not differ by variant location (Table 2: *BRCA1* P_{LRT}=0.17; *BRCA2* P_{LRT}≥0.27). However, the associations differed by the predicted effect of the gene variant on protein stability/expression: the HRs for the PRS associations with breast cancer risk were larger for carriers with class II (stable mutant proteins) *versus* class I (unstable/no protein) variants (Table 2, *BRCA1*: class I HR=1.26 (95%CI=1.22-1.30), class II HR=1.38 (1.30-1.46), $P_{difference}$=0.011; *BRCA2*: class I HR=1.30 (95%CI=1.25-1.35), class II HR=1.72 (95%CI=1.44-2.06), $P_{difference}$=0.003).

Under the age-varying PRS models, the C-statistic for PRS_{ER-} was 0.60 (95%CI=0.59-0.61) for *BRCA1* carriers, and for the PRS_{BC} for *BRCA2* carriers 0.65 (95%CI=0.63-0.67). Under models that did not include the age-varying PRS, the estimated C-statistics were 0.58 (95%CI=0.57-0.59) and 0.60 (95%CI=0.59-0.62) for *BRCA1* and *BRCA2* carriers, respectively.

Associations with ER-specific breast cancer risk

The strongest PRS associations with ER-negative disease were observed for PRS_{ER-} for both *BRCA1* (per SD HR=1.23, 95%CI=1.18-1.28, P=2x10^{-27}) and *BRCA2* (HR=1.31, 95%CI=1.21-1.43, P=1x10^{-10}) carriers (Table 1). The PRS_{BC} and PRS_{ER+} showed the strongest associations with ER-positive disease for *BRCA1* and *BRCA2* carriers with similar HR estimates for PRS_{BC} and PRS_{ER+} (Table 1). The associations remained similar after adjusting for family history of breast cancer (Table 1).

Associations with epithelial ovarian cancer risk

The 30-SNP PRS_{EOC}, was strongly associated with EOC risk for *BRCA1* (per SD HR=1.31, 95%CI=1.24-1.39, P=1x10^{-21}) and *BRCA2* (per SD HR=1.43, 95%CI=1.29-1.59, P=2x10^{-11})

carriers (Table 1). The 22-SNP PRS_{HGS}, based only on SNPs showing associations with high grade serous EOC, showed similar associations (Table 1, *BRCA1* HR=1.32, 95%CI=1.25-1.40, P=$3x10^{-22}$; *BRCA2* HR=1.44, 95%CI=1.30-1.60, P=$4x10^{-12}$). Adjusting for family history of ovarian cancer yielded similar associations to unadjusted models (Table 1).

PRS_{HGS} was used for downstream analyses for *BRCA1* and *BRCA2* carriers. There was no evidence of heterogeneity in the PRS_{HGS} associations across countries (Figure S3: *BRCA1* P_{LRT}=0.08; *BRCA2* P_{LRT}=0.97). For both *BRCA1* and *BRCA2* carriers the estimated HRs by PRS percentile categories (Table 2) were consistent with those expected under the theoretical population-based PRS distributions (Figures 1C and 1D). There was no evidence that the PRS_{HGS} association with EOC risk varied by age (*BRCA1* P=0.35; *BRCA2* P=0.14). The associations between PRS_{HGS} and EOC risk varied by *BRCA1* variant location (P_{LRT}=$8.7x10^{-3}$), with a larger HR for variants in the central region of *BRCA1* (central region HR=1.50, 95%CI=1.35-1.66; 5' to c.2281 region HR=1.30, 95%CI=1.18-1.42; c.4072 to 3' region HR=1.21, 95%CI=1.10-1.33). There was little evidence to support differences in the associations by *BRCA2* variant location (Table 2). There was no evidence of differences in the associations by the *BRCA1* variant predicted effect on protein expression ($P_{difference}$=0.85).

The C-statistics for PRS_{HGS} were estimated to be 0.604 (95%CI=0.582-0.626) for *BRCA1* and 0.667 (95%CI=0.636-0.699) for *BRCA2* carriers.

Prospective cohort associations

The breast cancer prospective cohort included 2,088 *BRCA1* carriers with 297 incident cases and 1,757 *BRCA2* carriers with 215 incident cases (Table S4). The PRS_{ER-} was associated with breast cancer risk for *BRCA1* carriers (per SD HR=1.28, 95%CI=1.14-1.44, P=$4.4x10^{-5}$). For *BRCA2* carriers, PRS_{BC} was associated with breast cancer risk with a per SD HR=1.36 (95%CI=1.17-1.57, P=$4.3x10^{-5}$) (Table 3).

The ovarian cancer prospective cohort comprised 3,152 *BRCA1* carriers with 108 incident cases and 2,495 *BRCA2* carriers with 56 incident cases (Table S4). The PRS_{HGS}

was associated with EOC risk for both *BRCA1* (HR=1.28, 95%CI=1.06-1.55, P=0.011) and *BRCA2* (HR=1.45, 95%CI=1.13-1.86, P=0.003) carriers (Table 3).

Absolute risks of cancer by PRS percentiles

We estimated age-specific and 10-year absolute risks of developing breast and ovarian cancers across different PRS percentiles (Figures 2 and S4). *BRCA1* carriers at the 5th and 95th percentiles of the PRS_{ER-} distribution were predicted to have breast cancer risks to age 80-years of 59% and 83%, respectively. The corresponding risks for *BRCA2* carriers based on PRS_{BC} were 57% and 81%. Although PRS associations were not altered by family history adjustment in the models, and there was no significant evidence of interaction between PRS and variant location, both of these factors remain significant predictors of breast cancer risk (in addition to PRS). Therefore, family history and variant location can be considered jointly with the PRS to predict cancer risks for *BRCA1*/*2* carriers (Figures S5-S9). For example, breast cancer risk to age 80-years for *BRCA2* carriers with no family history at the 5^{th} and 95^{th} percentiles of the PRS were predicted to be 43% and 67%, respectively, compared to 62% and 85% for those with a family history. The risks of developing ovarian cancer by age 80-years were 30% and 59% for *BRCA1* carriers at the 5th and 95th percentiles of the PRS_{HGS} distribution. The corresponding risks for *BRCA2* carriers were 10% and 28%, respectively.

DISCUSSION

We investigated the associations between a recently reported PRS for breast cancer, based on 313 SNPs, and a PRS for EOC, based on 30 SNPs, with cancer risks for *BRCA1* and *BRCA2* carriers. The associations were evaluated in a large retrospective cohort and separately in a prospective cohort of *BRCA1*/*2* carriers.

The results demonstrate that the PRS developed using population-based data are also associated with breast and ovarian cancer risk for women with *BRCA1*/*2* pathogenic

variants. The PRS developed for predicting ER-negative breast cancer showed the strongest association with breast cancer risk for *BRCA1* carriers, while for *BRCA2* carriers the PRS developed for predicting overall breast cancer risk performed best. The associations were unchanged after adjusting for cancer family history and were similar between the retrospective and prospective studies. There was evidence that the magnitude of the PRS associations decreased with increasing age for *BRCA1* and *BRCA2* carriers. There was evidence for differences in associations by the predicted effects of variants on protein stability/expression, with the breast cancer PRS having a larger effect for carriers of variants predicted to yield a stable protein. For ovarian cancer, the PRS developed for predicting overall or HGS EOC demonstrated similar evidence of association with EOC risk, for both *BRCA1* and *BRCA2* carriers. The results are consistent with findings from a previous CIMBA study, based on fewer samples and fewer SNPs, which demonstrated that PRS can lead to large differences in absolute risks of developing breast and ovarian cancers for female *BRCA1*/*2* carriers[10].

The estimated HR associations for the PRS with breast cancer risk from this study were smaller than the estimated ORs from the population-based study in which they were derived[12]. This difference is unlikely to be an overestimation of the ORs in the general population ("winner's curse"[26]), because the effect sizes were estimated in prospective studies which were independent of the data used in their development[12,27]. Adjustment for family history, a potential confounder in this study, did not influence the associations. Therefore, these most likely represent real differences, in which PRS modify breast cancer risk for *BRCA1*/*2* carriers to a smaller relative extent than the general population. This meaningful attenuation must be considered when using population-based PRS to predict breast cancer risk for *BRCA1*/*2* carriers and should be incorporated into breast cancer risk prediction models[28].

The departure from the multiplicative model for the joint effects of PRS (or some subset of SNPs) and *BRCA*/*2* pathogenic variants might simply reflect the high absolute risks for *BRCA1*/*2* carriers. That is, women with the highest polygenic risk are likely to

develop breast cancer at a young age, so that the relative risk associated with the PRS will diminish with age. It is interesting that the decreasing age effect appeared stronger for carriers than the general population, while the relative risk below age 50-years was more comparable to that seen in the general population[12]. We found that the breast cancer HRs were significantly elevated for carriers of variants that are predicted to generate a stable mutant protein ("class II" variants). These elevated HRs were similar to the corresponding ORs for association between the PRS and ER-negative (OR=1.47) and ER-positive (OR=1.74) breast cancer reported in the general population[12]. The vast majority of individuals in the general population would be expected to be non-carriers with intact BRCA1/2 protein expression in at-risk tissues, so this observation suggests that some SNPs in the PRS may exert their effect on proteins that interact with stable wildtype or mutant BRCA1 or BRCA2 protein.

We used the ER-specific PRS to assess associations with ER-positive and ER-negative breast cancer for *BRCA1*/*2* carriers. As expected, the PRS developed for ER-positive breast cancer in the general population was the most predictive of ER-positive breast cancer risk for both *BRCA1* and *BRCA2* carriers, and the PRS developed for ER-negative breast cancer was the most predictive of ER-negative breast cancer for both *BRCA1* and *BRCA2* carriers, in line with known differences in ER expression between *BRCA1*- and *BRCA2*-related tumours[29,30]. These results suggest that further risk prediction improvements can be achieved by estimating the risk of developing ER-specific breast cancer for *BRCA1*/*2* carriers.

Unlike the breast cancer PRS, no systematic evaluation of EOC PRS has been reported in the general population. We therefore included only SNPs identified through GWAS for EOC and its histotypes, using the reported effect sizes as PRS weights. We found that a PRS constructed on the basis of the associations between SNPs and HGS EOC was the most predictive for both *BRCA1* and *BRCA2* carriers, in line with the fact that the majority of tumours in both *BRCA1* and *BRCA2* carriers are HGS[15]. The estimated HR for PRS_{HGS} was larger for *BRCA2* carriers compared with the *BRCA1* carrier HR estimate. This pattern

had been observed previously, based on a smaller sample size and fewer SNPs, but the difference between the HRs observed here is smaller than that reported previously[10].

Predicted absolute risks for *BRCA1* carriers at the 5th and 95th PRS percentiles at age 50-years varied from 31% to 58% for breast, and from 5% to 13% for ovarian cancer. By age 80-years, they varied from 59% to 83% for breast and from 30% to 59% for ovarian cancer. The corresponding absolute risks for *BRCA2* carriers by age 50-years ranged from 23% to 49% and by age 80-years from 57% to 81% for breast cancer. The ovarian cancer risks by age 80-years varied from 10% to 28%. We also observed differences in the 10-year age-specific risks of cancer for different PRS distribution percentiles (Figure S4). For example, the estimated 10-year risk of developing breast cancer at age 40-years was 17% and 34% for *BRCA1* carriers at the 5th and 95th percentiles of the PRS for ER-negative breast cancer, respectively. We found no significant attenuation of the PRS associations when adjusting for family history, and no evidence of interaction between PRS and pathogenic variant location. However, family history and variant location are both associated with cancer risk for *BRCA1*/*2* carriers[2,20-22]. Taken together, the results suggest that when family history and PRS are considered jointly, or when variant location and PRS are considered jointly, both factors influence the risk of developing breast cancer for *BRCA1*/*2* carriers. As a consequence, the differences in absolute risk become larger when the PRS is considered together with family history or variant location (Figures S5-S9) and demonstrate that the PRS should be considered in combination with other risk factors to provide comprehensive cancer risks for *BRCA1*/*2* carriers.

Strengths of this study include the large cohort sample sizes of *BRCA1*/*2* carriers and use of independent prospective cohort data to validate PRS associations with cancer risks. The similarity in association estimates between the retrospective and prospective analyses suggests that retrospective estimates have not been strongly influenced by potential biases (e.g. survival bias). As the PRS analysed in this study were originally developed and validated in population-based studies, the associations reported here represent independent evaluations of the PRS in *BRCA1*/*2* carriers. The analyses were also adjusted for cancer

family history, hence associations are unlikely to be biased due to confounding.

Limitations of this study include the fact that tumour ER-status information was missing on a substantial proportion of the study population. Therefore, we were unable to assess associations with ER-specific breast cancer in the entire sample of *BRCA1*/*2* carriers. The use of PRS developed in the general population means that if there are *BRCA1*- or *BRCA2*-specific modifier SNPs[4,5], these may not have been included in the PRS. Therefore, alternative approaches should also investigate developing PRS using data directly from *BRCA1* and *BRCA2* carriers, although much larger sample sizes will be required. We did not present confidence intervals for the predicted PRS-specific absolute risks of breast or ovarian cancer, and the absolute PRS-specific risks by variant location and family history. These predictions critically depend on external cancer incidence estimates for *BRCA1*/*2* pathogenic variant carriers[2] which themselves are uncertain and therefore should only be used as a general guide. Future studies should aim to factor in uncertainty in the predicted risks based on all parameters. In addition, the PRS-specific absolute cancer risks overall and by family history or pathogenic variant location should be validated in much larger prospective studies of unaffected carriers. Finally, the present analyses were limited to carriers of European ancestry. Hence the results presented may not be applicable to *BRCA1*/*2* carriers of Asian, African, and other non-European ancestries.

PRS are now being used in risk-stratified screening trials and other implementation studies in the general population[31]. They are commercially available and have been incorporated in comprehensive cancer risk prediction models[28,32]. The findings of this study indicate that these PRS, in combination with established risk modifiers (e.g. family history and pathogenic variant characteristics) can be used to provide more personalised cancer risk predictions for carriers, which may assist clinical management decisions. It is therefore important to undertake relevant implementation studies to determine the optimal way of incorporating these PRS into genetic counselling and risk management, and to assess whether PRS on their own or in combination with other risk factors influence the short- or long-term clinical management decisions that female *BRCA1*/*2* carriers make. Furthermore,

the available risk models incorporating the effects of *BRCA1*/*2* pathogenic variants[28,32] and PRS should be validated in large prospective studies of carriers.

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APPENDIX

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FIGURE LEGENDS

Figure 1: Associations with specific PRS percentiles.

The PRS percentile thresholds were determined in the sets of unaffected carriers for the disease under assessment. Table 2 shows the estimated HRs. The black dashed curve represents the expected HRs assuming the per standard deviation HR estimates in *BRCA1* and *BRCA2* carriers based on the continuous PRS models (Table 1). (A) PRS_{ER-} percentile specific associations with breast cancer risk for *BRCA1* carriers. The red dashed curve represents the expected HRs over the PRS percentile distribution, assuming the per SD OR estimate from the population-based validation studies from Mavaddat et al [12] (OR=1.45 per PRS_{ER-} standard deviation). (B) PRS_{BC} percentile specific associations with breast cancer risk for *BRCA2* carriers. The red dashed curve represents the expected HRs over the PRS percentile distribution, assuming the per SD OR estimate from the population-based validation studies from Mavaddat et al [12] (OR=1.61 per PRS_{BC} standard deviation). (C) PRS_{HGS} percentile specific associations with ovarian cancer risk for *BRCA1* carriers. (D) PRS_{HGS} percentile specific associations with ovarian cancer risk for *BRCA2* carriers. The grey dashed curve (plots C and D only) represents the theoretical HRs across the PRS distribution, calculated by assuming external SNP effect sizes and allele frequencies for SNPs contributing to the PRS.

Figure 2: Predicted absolute risks of developing breast and ovarian cancer by PRS percentile.

Risks were calculated assuming the retrospective cohort HR estimates (Tables 1-2). (A) Predicted absolute risks of developing breast cancer for *BRCA1* carriers by percentiles of the PRS_{ER-}. (B) Predicted absolute risks of developing breast cancer for *BRCA2* carriers by percentiles of the PRS_{BC}. (C) Predicted absolute risks of developing ovarian cancer for *BRCA1* carriers by percentiles of the PRS_{HGS}. (D) Predicted absolute risks of developing ovarian cancer for *BRCA2* carriers by percentiles of the PRS_{HGS}.

Table 1. PRS associations with breast and ovarian cancer risks for *BRCA1* and *BRCA2* pathogenic variant carriers using the CIMBA retrospective cohort data.

		***BRCA1* carriers**					***BRCA2* carriers**				
			No FH adjustment		*FH adjusted*			*No FH adjustment*		*FH adjusted*	
Outcome	**PRS**	Unaffected/ Affected	HR (95% CI)	P	HR (95% CI)	P	Unaffected/ Affected	HR (95% CI)	P	HR (95% CI)	P
Breast cancer	BC	9462/ 9473	1.20 (1.17-1.23)	$1.15x10^{-39}$	1.20 (1.17-1.23)	$9.54x10^{-40}$	6007/ 6332	**1.31 (1.27-1.36)**	**$7.11x10^{-50}$**	**1.31 (1.26-1.36)**	**$6.54x10^{-48}$**
	ER-		**1.29 (1.25-1.33)**	**$3.03x10^{-72}$**	**1.29 (1.25-1.33)**	**$1.02x10^{-71}$**		1.23 (1.19-1.28)	$4.06x10^{-29}$	1.23 (1.18-1.27)	$6.72x10^{-28}$
	ER+		1.17 (1.14-1.20)	$6.93x10^{-29}$	1.17 (1.14-1.20)	$5.50x10^{-29}$		1.31 (1.26-1.36)	$6.12x10^{-49}$	1.30 (1.26-1.35)	$5.10x10^{-47}$
ER-negative breast cancer	BC	10138/ 3263	1.09 (1.05-1.13)	$3.69x10^{-6}$	1.09 (1.05-1.13)	$4.44x10^{-6}$	8049/ 703	1.20 (1.11-1.30)	$4.90x10^{-6}$	1.19 (1.10-1.29)	$1.91x10^{-5}$
	ER-		**1.23 (1.18-1.28)**	**$2.39x10^{-27}$**	**1.23 (1.18-1.27)**	**$1.08x10^{-26}$**		**1.31 (1.21-1.43)**	**$1.15x10^{-10}$**	**1.29 (1.19-1.41)**	**$9.98x10^{-10}$**
	ER+		1.06 (1.02-1.10)	$4.58x10^{-3}$	1.06 (1.02-1.10)	$4.93x10^{-3}$		1.17 (1.08-1.26)	$1.36x10^{-4}$	1.15 (1.07-1.25)	$3.91x10^{-4}$
ER-positive breast cancer	BC	12376/ 1025	**1.44 (1.35-1.53)**	**$3.88x10^{-28}$**	**1.44 (1.35-1.54)**	**$1.25x10^{-27}$**	6440/ 2312	1.37 (1.31-1.44)	$2.95x10^{-40}$	1.36 (1.30-1.43)	$6.28x10^{-38}$
	ER-		1.29 (1.21-1.38)	$2.94x10^{-15}$	1.29 (1.21-1.37)	$9.25x10^{-15}$		1.22 (1.16-1.28)	$1.93x10^{-15}$	1.21 (1.15-1.27)	$1.54x10^{-14}$
	ER+		1.44 (1.35-1.54)	$3.94x10^{-28}$	1.45 (1.35-1.54)	$1.12x10^{-27}$		**1.38 (1.32-1.45)**	**$1.88x10^{-42}$**	**1.37 (1.31-1.44)**	**$5.99x10^{-40}$**
Ovarian cancer	EOC	16867/ 2068	1.31 (1.24-1.39)	$1.49x10^{-21}$	1.31 (1.24-1.39)	$2.36x10^{-21}$	11621/ 718	1.43 (1.29-1.59)	$1.81x10^{-11}$	1.42 (1.28-1.58)	$3.40x10^{-11}$
	HGS		**1.32 (1.25-1.40)**	**$3.01x10^{-22}$**	**1.32 (1.25-1.40)**	**$5.18x10^{-22}$**		**1.44 (1.30-1.60)**	**$4.34x10^{-12}$**	**1.43 (1.29-1.59)**	**$7.54x10^{-12}$**

BC = breast cancer; ER- = estrogen-receptor negative; ER+ = estrogen-receptor positive; EOC = epithelial ovarian cancer; HGS = high-grade serous.

FH = family history: coded as no family history, or one relative, or two or more relatives diagnosed with the disease.

HR = hazard ratio; CI = confidence interval; P = P-value.

Table 2. Categorical PRS, age-varying and pathogenic variant characteristic specific PRS associations with cancer risks for *BRCA1* and *BRCA2* carriers, using data from the CIMBA retrospective cohort.

		Breast cancer						**Ovarian cancer**					
		***BRCA1* carriers: PRS_{ER-}**			***BRCA2* carriers: PRS_{BC}**			***BRCA1* carriers: PRS_{HGS}**			***BRCA2* carriers: PRS_{HGS}**		
Model	**Category**	HR (95% CI)	P	P_{LRT}	HR (95% CI)	P	P_{LRT}	HR (95% CI)	P	P_{LRT}	HR (95% CI)	P	P_{LRT}
Categorical PRS Percentiles (%)	0-5	0.59 (0.50-0.70)			0.52 (0.42-0.64)			0.68 (0.50-0.92)			0.40 (0.20-0.79)		
	5-10	0.69 (0.59-0.80)			0.60 (0.49-0.73)			0.80 (0.59-1.09)			0.47 (0.24-0.91)		
	10-20	0.77 (0.69-0.86)			0.69 (0.59-0.80)			1.01 (0.81-1.26)			0.53 (0.33-0.85)		
	20-40	0.91 (0.84-1.00)			0.82 (0.73-0.92)			0.96 (0.80-1.15)			0.83 (0.60-1.14)		
	40-60	1.00 [reference]			1.00 [reference]			1.00 [reference]			1.00 [reference]		
	60-80	1.12 (1.03-1.21)			1.05 (0.94-1.18)			1.16 (0.97-1.39)			0.97 (0.71-1.33)		
	80-90	1.38 (1.25-1.53)			1.21 (1.06-1.38)			1.57 (1.28-1.91)			1.38 (0.95-2.00)		
	90-95	1.55 (1.37-1.75)			1.44 (1.21-1.71)			1.86 (1.44-2.41)			1.36 (0.86-2.15)		
	95-100	1.61 (1.43-1.82)			1.69 (1.45-1.98)			2.24 (1.76-2.84)			2.03 (1.31-3.15)		
Age-varying PRS[a]: model including a main PRS effect and a PRSxAge interaction term	PRS	1.517 (1.359-1.694)	$1.04x10^{-13}$	0.017	1.721 (1.498-1.977)	$1.75x10^{-14}$	$2.27x10^{-3}$	1.507 (1.125-2.020)	$6.02x10^{-3}$	0.41	2.183 (1.263-3.774)	$5.17x10^{-3}$	0.44
	PRS x age	0.996 (0.993-0.999)	$3.27x10^{-3}$		0.994 (0.991-0.997)	$9.40x10^{-5}$		0.997 (0.991-1.003)	0.35		0.992 (0.982-1.003)	0.14	
Gene pathogenic variant class	Class I	1.26 (1.22-1.30)	0.011[b]	$5.29x10^{-3}$	1.30 (1.25-1.35)	$3.20x10^{-3}$[b]	0.046	1.33 (1.24-1.43)	0.85[b]	0.85	N/A[c]		
	Class II	1.38 (1.30-1.46)			1.72 (1.44-2.06)			1.32 (1.18-1.47)					
BRCA1 pathogenic variant location	c.2282-c.4071	1.25 (1.19-1.31)		0.17	N/A			1.50 (1.35-1.66)		$8.73x10^{-3}$	N/A		
	5' to c.2281	1.28 (1.22-1.34)						1.30 (1.18-1.42)					
	c.4072 to 3'	1.34 (1.28-1.41)						1.21 (1.10-1.33)					
BRCA2 pathogenic variant location (narrow)	c.3847-c.6275	N/A			1.30 (1.23-1.38)		0.27	N/A			1.48 (1.24-1.76)		0.96
	5' to c.3846				1.26 (1.17-1.34)						1.41 (1.17-1.69)		
	c.6276 to 3'				1.37 (1.29-1.46)						1.43 (1.20-1.70)		
BRCA2 pathogenic variant location (wide)	c.2831-c.6401	N/A			1.29 (1.23-1.36)		0.33	N/A			1.48 (1.26-1.75)		0.90
	5' to c.2830				1.26 (1.17-1.37)						1.37 (1.13-1.68)		
	c.6402 to 3'				1.37 (1.29-1.46)						1.43 (1.20-1.71)		

ER- = estrogen-receptor negative; BC = breast cancer; HGS = high-grade serous.

HR = hazard ratio; CI = confidence interval; P = P-value for the Wald test statistic unless otherwise stated; LRT = likelihood ratio test comparing the models with an interaction term against the model without the interaction term; N/A = not applicable.

“Class I” pathogenic variant = loss-of-function pathogenic variants expected to result in unstable or no protein; “class II” pathogenic variant = pathogenic variants likely to yield stable mutant proteins.

[a] Age in years.

[b] P-value for the difference in HR for “class I” carriers vs the HR for “class II” carriers.

[c] Number of affected “class II” carriers was too small to make meaningful inference.

Table 3. Associations of the best performing PRS in the prospective cohort of *BRCA1* and *BRCA2* carriers.

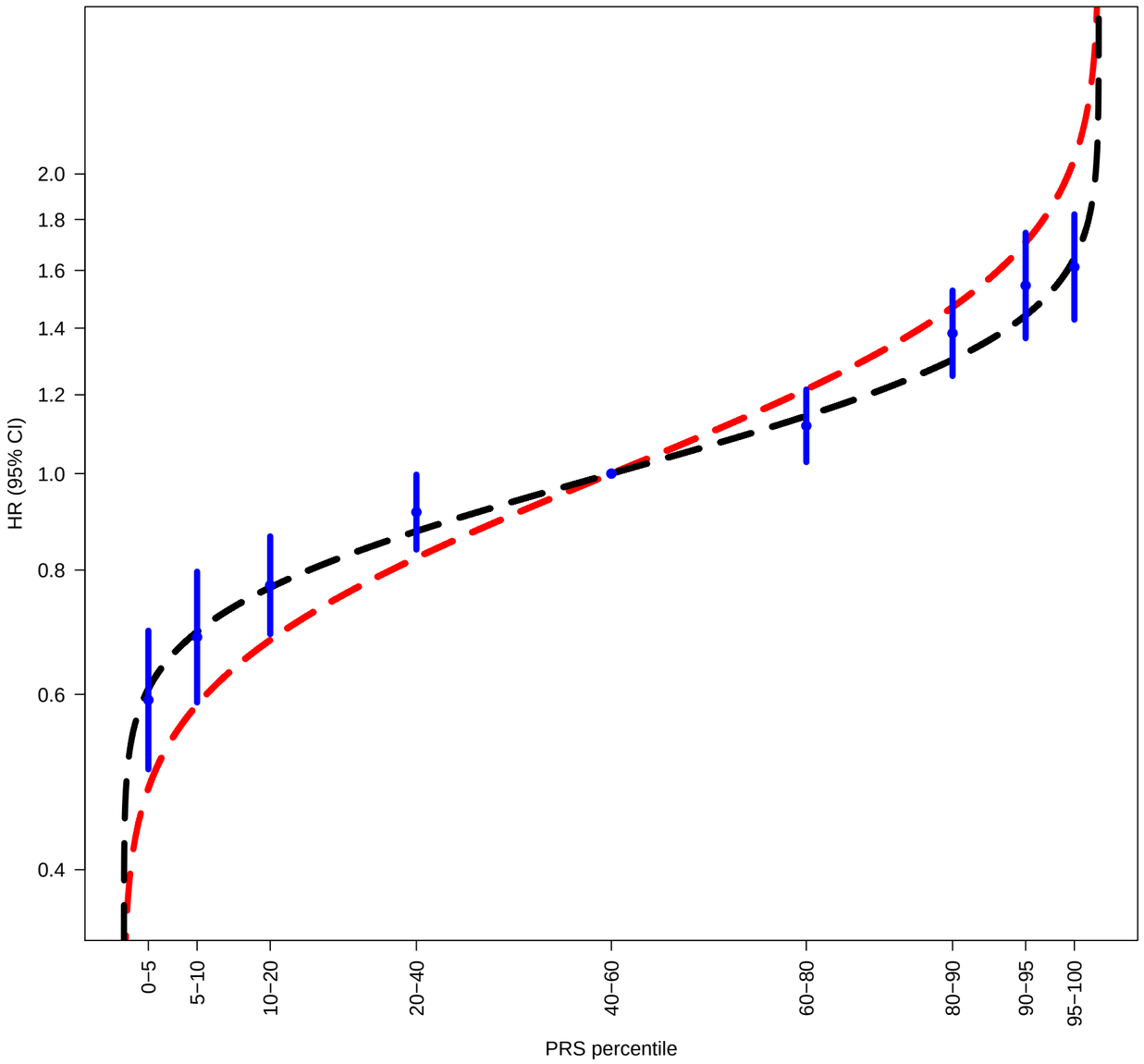
Outcome		**PRS**	**Number of women at risk**	**Incident cancers**	**HR (95% CI)**	**P**
Breast cancer	*BRCA1* carriers	ER-	2088	297	1.28 (1.14-1.44)	4.44×10^{-5}
	BRCA2 carriers	BC	1757	215	1.36 (1.17-1.57)	4.26×10^{-5}
Ovarian cancer	*BRCA1* carriers	HGS	3152	108	1.28 (1.06-1.55)	1.08×10^{-2}
	BRCA2 carriers	HGS	2495	56	1.45 (1.13-1.86)	3.29×10^{-3}

Number of women at risk is the number of pathogenic variant carriers unaffected at baseline. Incident cancers is the number of women who developed breast/ovarian cancer during the follow-up period.

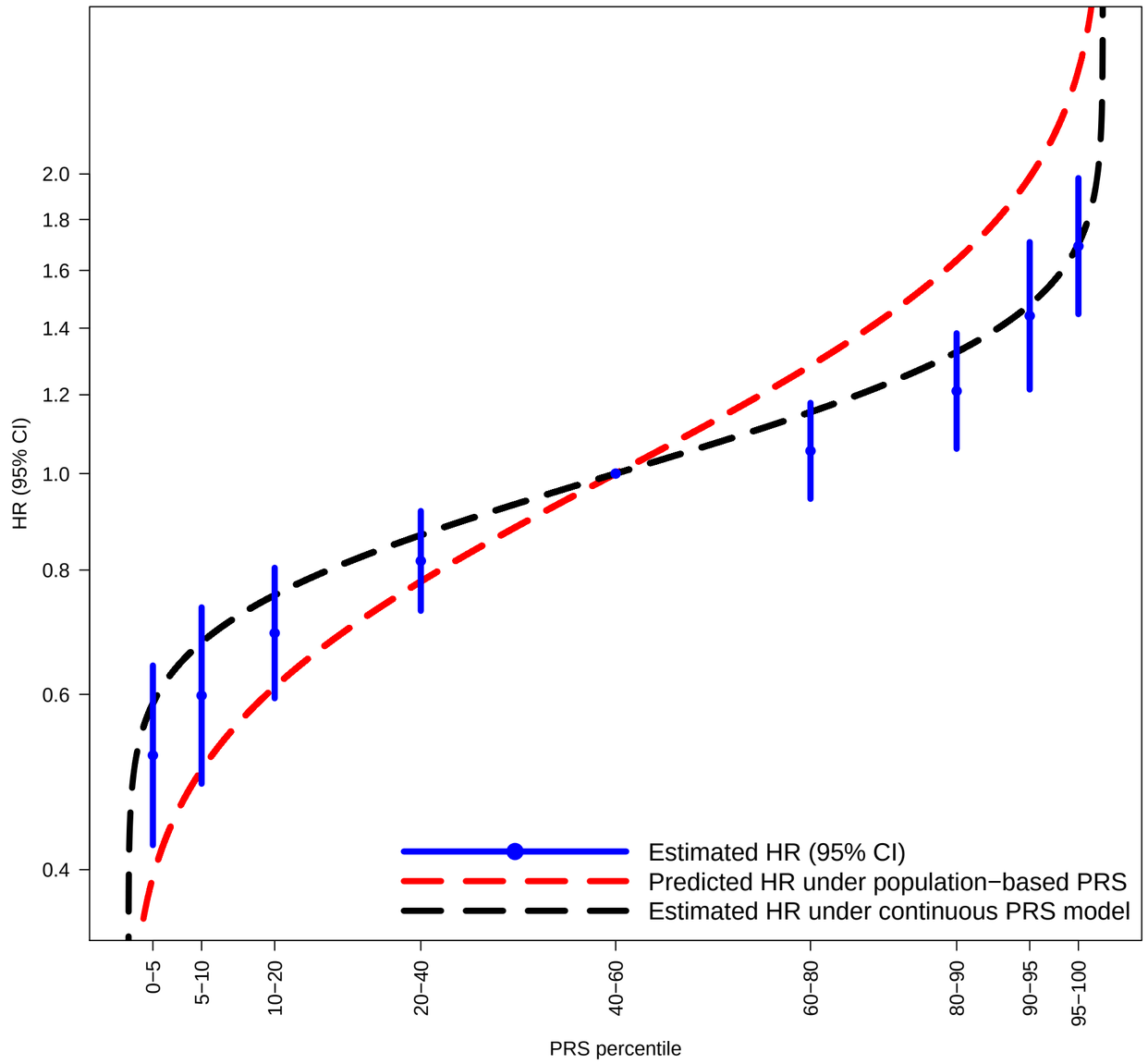
ER- = estrogen-receptor negative; BC = breast cancer; HGS = high-grade serous.

HR = hazard ratio; CI = confidence interval; P = P-value.

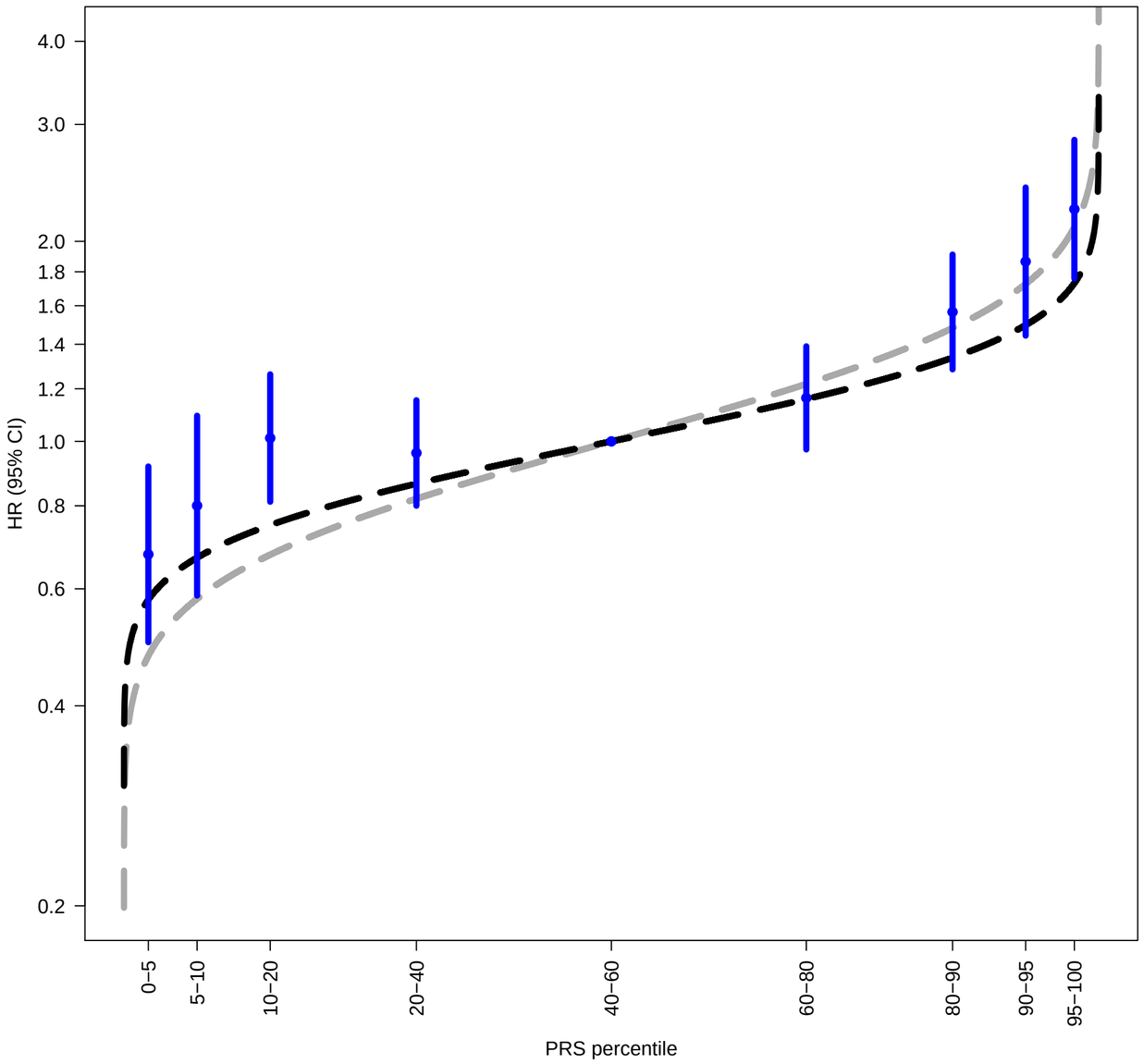
(A) BRCA1 carriers: ER−negative PRS



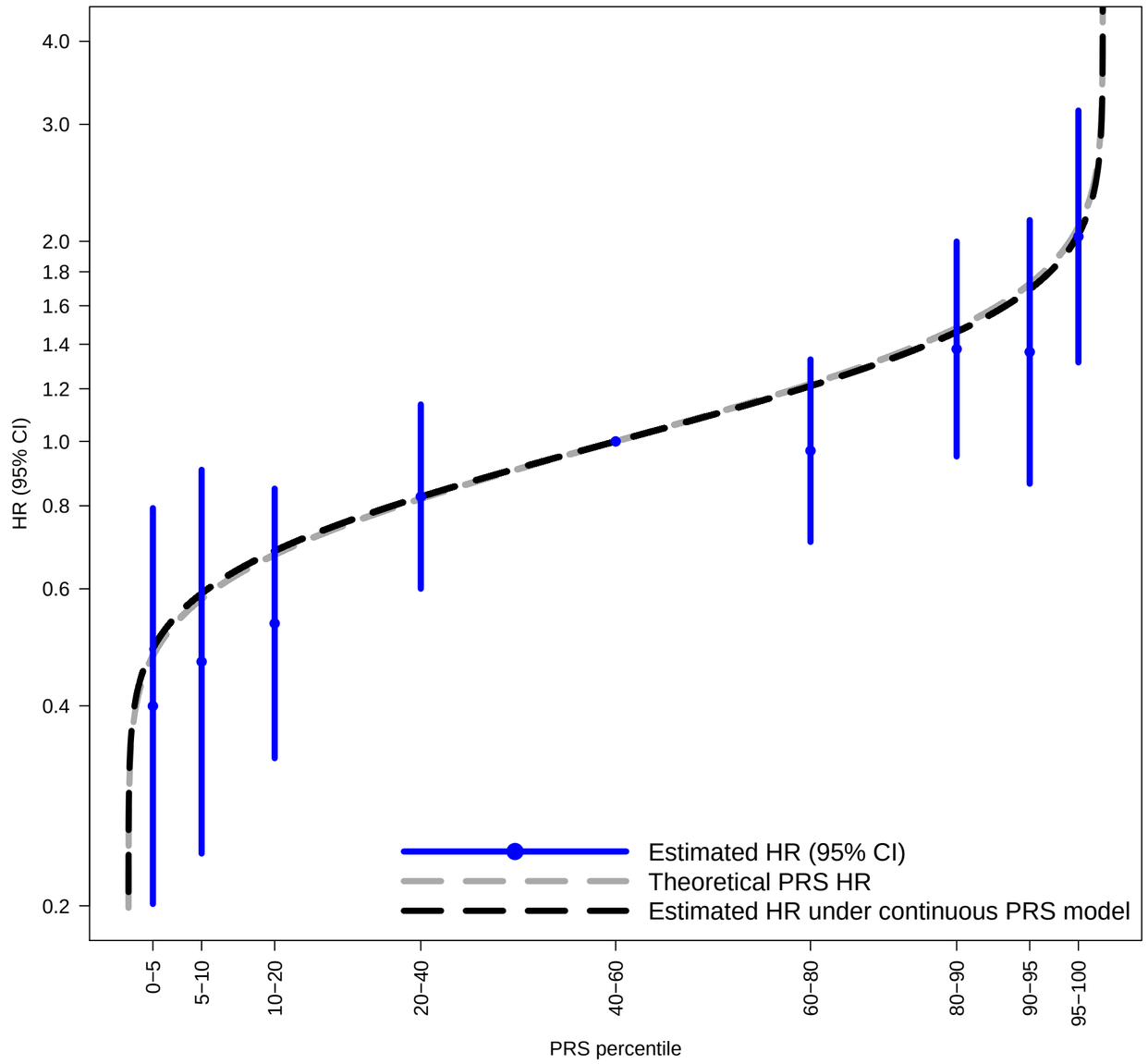
(B) BRCA2 carriers: Overall PRS



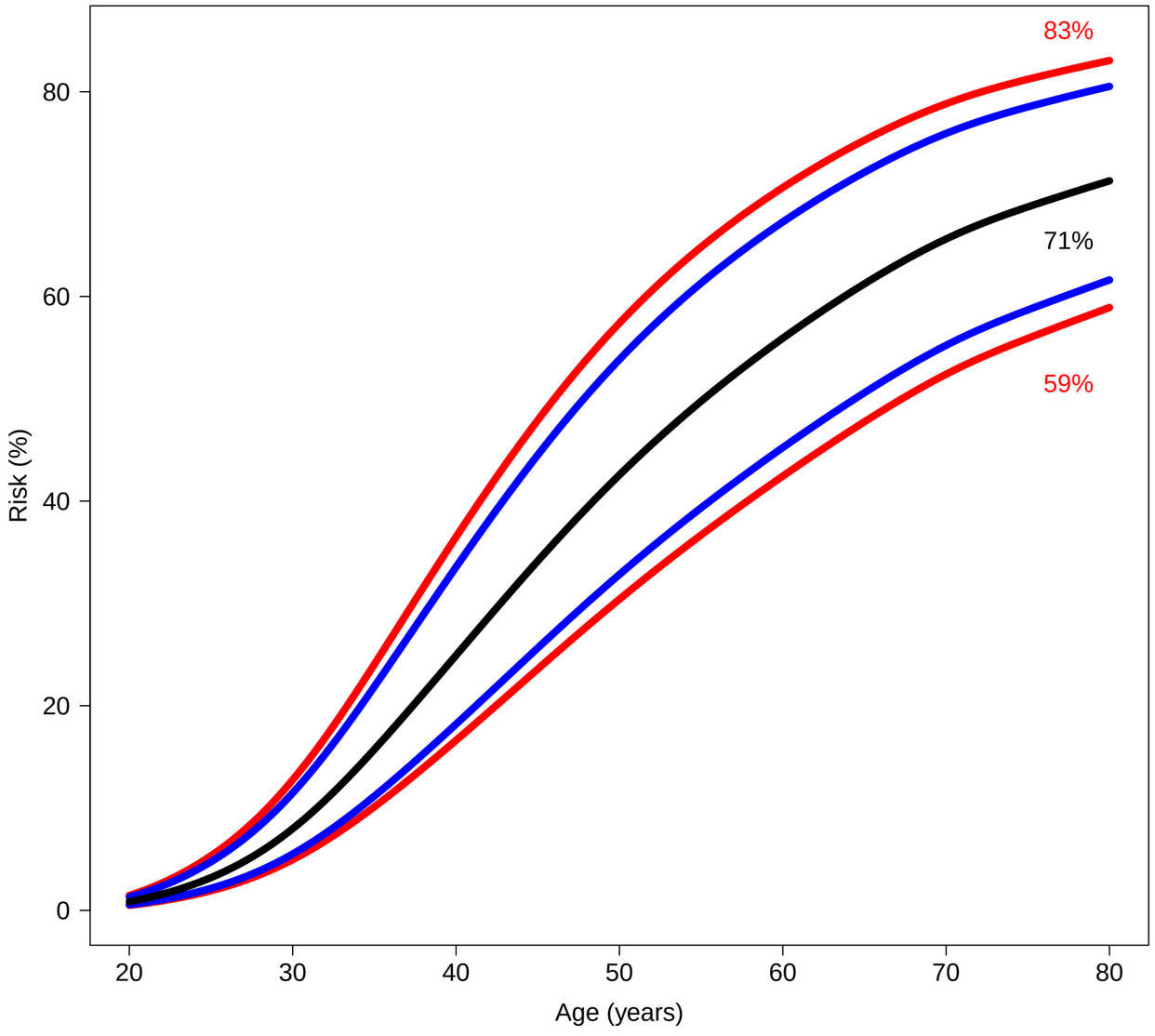
(C) BRCA1 carriers: HGS PRS



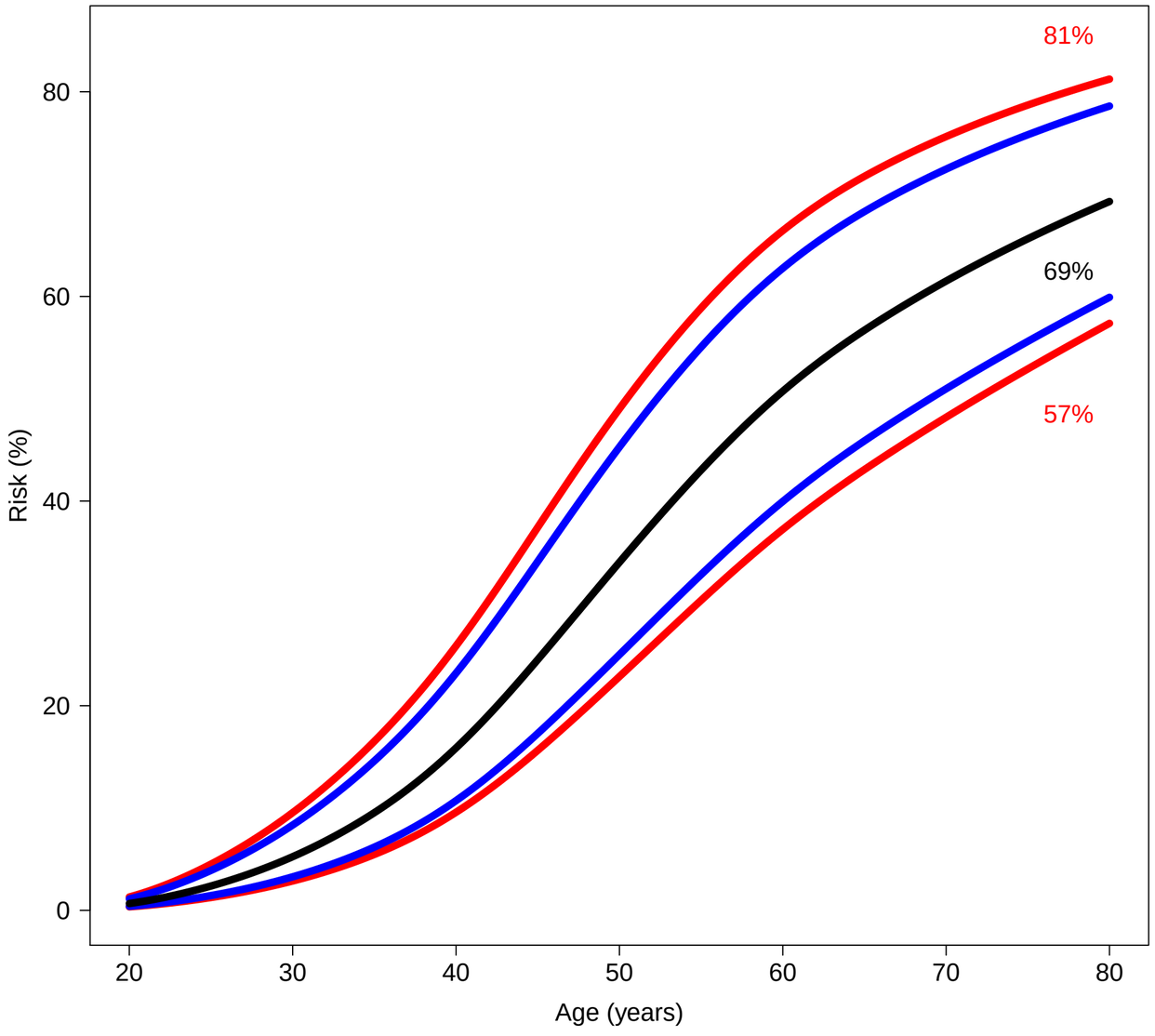
(D) BRCA2 carriers: HGS PRS



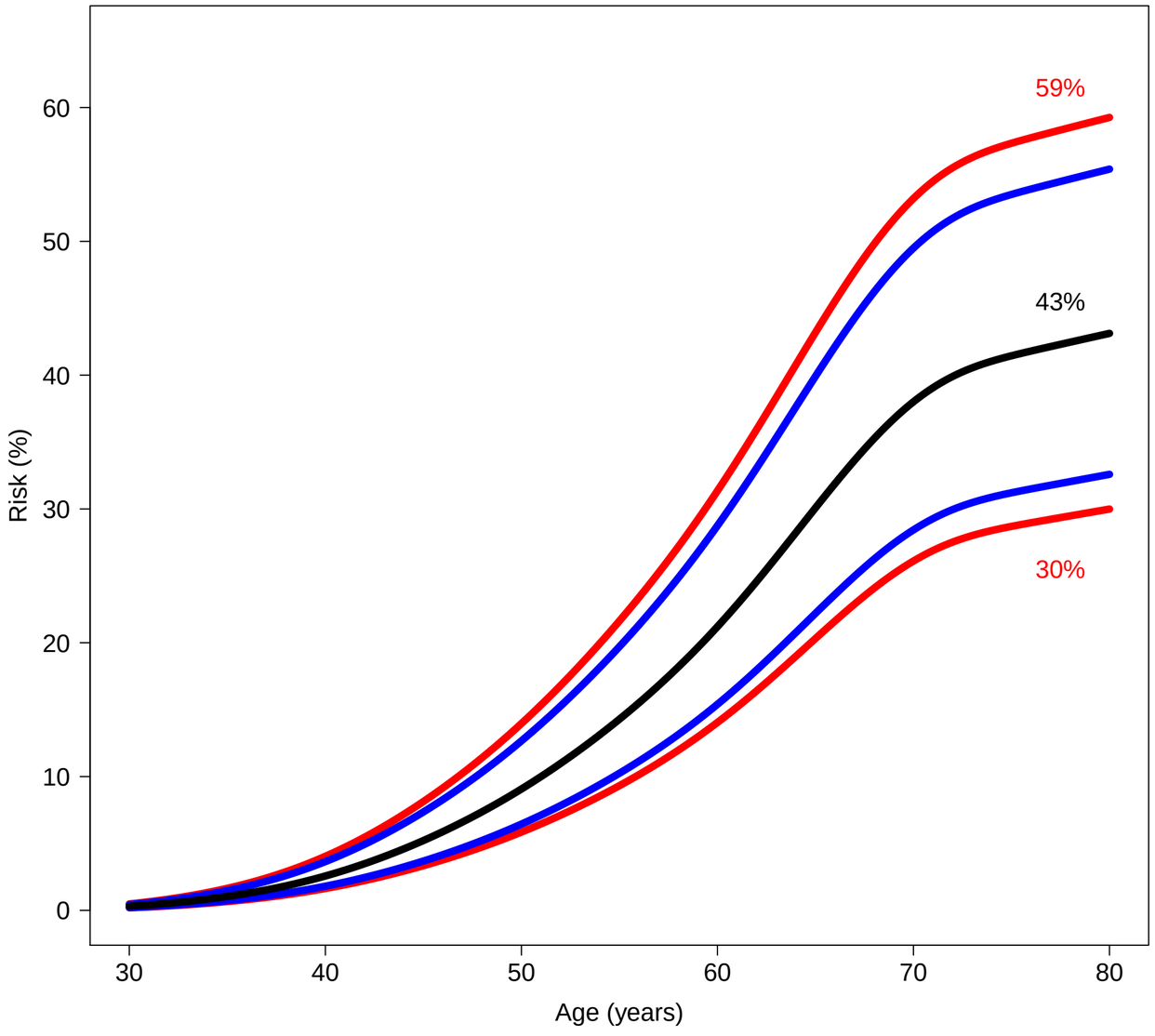
(A) BRCA1 carriers: ER−negative PRS



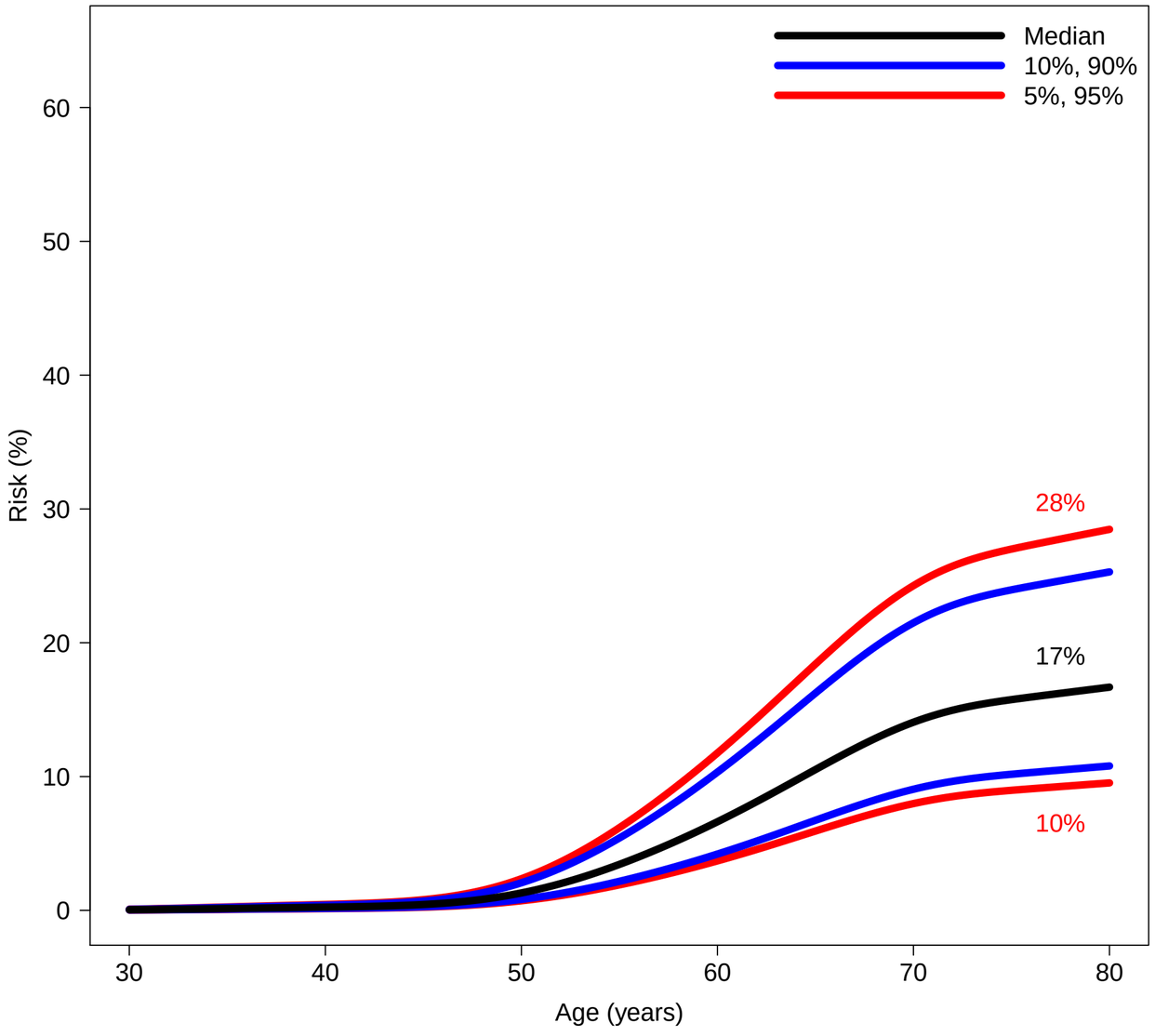
(B) BRCA2 carriers: Overall PRS



(C) BRCA1 carriers: HGS PRS



(D) BRCA2 carriers: HGS PRS



SUPPLEMENTARY MATERIAL

Ethics Statement

All study participants provided written informed consent and participated in research or clinical studies at the host institute under ethically approved protocols. The studies and their approving institutes are: Australian site of the Breast Cancer Family Registry (BCFR-AU) - The University of Melbourne Health Sciences Human Ethics Sub-Committee; Northern California site of the Breast Cancer Family Registry (BCFR-NC) - Northern California Cancer Center Institutional Review Board; New York site of the Breast Cancer Family Registry (BCFR-NY) - Columbia University Medical Center Institutional Review Board; Ontario site of the Breast Cancer Family Registry (BCFR-ON) - Mount Sinai Hospital Research Ethics Board; Philadelphia site of the Breast Cancer Family Registry (BCFR-PA) - Institutional Review Board Fox Chase Cancer Center; Utah site of the Breast Cancer Family Registry (BCFR-UT) - Institutional Review Board University of Utah; Baltic Familial Breast and Ovarian Cancer Consortium (BFBOCC) - Centrālā medicīnas ētikas Komiteja; Lietuvos Bioetikos Komitetas; BRCA-gene mutations and breast cancer in South African women (BMBSA) - University of Pretoria and Pretoria Academic Hospitals Ethics Committee; Beckman Research Institute of the City of Hope (BRICOH) - City of Hope Medical Center Institutional Review Board; Copenhagen Breast Cancer Study (CBCS) - De Videnskabsetiske Komiteer I Region Hovedsladen; Spanish National Cancer Centre (CNIO) - Instituto de Salud Carlos III Comité de Bioética y Bienestar Animal; City of Hope Cancer Center (COH) - City of Hope Institutional Review Board; CONsorzio Studi ITaliani sui Tumori Ereditari Alla Mammella (CONSIT TEAM) - Comitato Etico Indipendente della Fondazione IRCCS "Istituto Nazionale dei Tumori"; National Centre for Scientific Research Demokritos (DEMOKRITOS) - Bioethics committee of NCSR ‘‘Demokritos’’, 240/ΕΗΔ/11.3; National Centre for Scientific Research Demokritos (DEMOKRITOS) - Papageorgiou Hospital Ethics Committee; Dana Farber Cancer Institute (DFCI) - Dana Farber Cancer Institute Institutional Review Board; Deutsches Krebsforschungszentrum (DKFZ) - Ethik-Kommission des

Klinikums der Universität; Deutsches Krebsforschungszentrum (DKFZ) - Hospital Universitario de San Ignacio Comité de Investigaciones y Etica; Deutsches Krebsforschungszentrum (DKFZ) - Shaukat Khanum Memorial Cancer Hospital and Research Centre Institutional Review Board; Epidemiological study of BRCA1 and BRCA2 mutation carriers (EMBRACE) - Anglia & Oxford MREC; Fox Chase Cancer Center (FCCC) - Institutional Review Board Fox Chase Cancer Center; Fundación Pública Galega de Medicina Xenómica - Comite Autonomico de Etica da Investigacion de Galicia; German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) - Ethik-Kommission der Medizinischen Fakultät der Universät zu Köln; Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers (GEMO) - Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé; Georgetown University (GEORGETOWN) - MedStar Research Institute - Georgetown University Oncology Institutional Review Board; Ghent University Hospital (G-FAST) - Universitair Ziekenhuis Gent - Ethics Committee; Hospital Clinico San Carlos (HCSC) - Comité Ético de Investigación Clínia Hospital Clínico San Carlos; Helsinki Breast Cancer Study (HEBCS) - Helsingin ja uudenmaan sairaanhoitopiiri (Helsinki University Central Hospital ethics committee); HEreditary Breast and Ovarian study Netherlands (HEBON) - Protocol Toetsingscommissie van het Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis; Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary (HUNBOCS) - Institutional Review Board of the Hungarian National Institute of Oncology; University Hospital Vall d'Hebron (HVH) - The Hospital Universitario Vall d'Hebron Clinical Research Ethics Committee; Institut Català d'Oncologia (ICO) - Catalan Institute of Oncology Institutional Review Board; International Hereditary Cancer Centre (IHCC) - Komisji Bioetycznej Pomorskiej Akademii Medycznej (Pomeranian Medical University Bioethics Committee); Iceland Landspitali - University Hospital (ILUH) - Vísindasiðanefnd National Boethics Committee; Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT) - Comité d'éthique de la recherche du Centre Hospitalier Universitaire de Québec; Istituto Oncologico Veneto Hereditary Breast and Ovarian Cancer Study (IOVHBOCS) - Centro Oncologico Regionale

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Genotyping and SNP imputation

Genotyping was performed on one of two bespoke SNP arrays. The majority of the samples were genotyped using the OncoArray (15,679 *BRCA1* and 10,981 *BRCA2* carriers)[1-3]. The OncoArray is a custom genotyping array comprising approximately 533,000 SNPs, including a GWAS backbone component tagging common SNPs across the genome which accounted for approximately half of the SNPs on the array. The remaining 3,256 (17.2%) *BRCA1* and 1,358 (11.0%) *BRCA2* pathogenic variant carriers were genotyped using the iCOGS array[4,5] which included approximately 210,000 SNPs selected primarily on the basis of evidence of association with breast, ovarian and prostate cancers.

A standard quality control (QC) process was applied for samples genotyped on both arrays, which included assessment of the SNP call rate, allele frequency, genotyping intensity clustering metrics, Hardy-Weinberg equilibrium and SNP concordance in duplicate samples[2]. Two-stage imputation was performed using SHAPEIT software[6] for phasing and IMPUTE2 software[7] for imputation using the 1000 Genomes Project (Phase 3) reference

panel.

SNPs were included in the PRS if they were adequately imputed in the CIMBA data. The imputation accuracy was assessed using the r^2 statistic, based on the "info" statistic produced by the IMPUTE2 software (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html#info_metric_details)[7]. This statistic takes values from 0 (complete uncertainty of imputed genotypes) to 1 (no uncertainty of imputed genotypes). The r^2 values for the SNPs used in the current analyses are listed in Tables S1 and S2 and shown in Figures S1 and S2.The minimum r^2 values among the 313 SNPs in the breast cancer PRS were 0.49 for samples genotyped on iCOGS and 0.90 for samples genotyped on OncoArray. For the 30 SNPs in the ovarian cancer PRS, the minimum r^2 was 0.64 for iCOGS samples and 0.88 for OncoArray samples.

Principal components analysis

To adjust for potential (intra-continental) population stratification in the OncoArray dataset, principal components analysis was performed using data from 33,661 uncorrelated SNPs (which included 2,318 SNPs specifically selected on informativeness for determining continental ancestry) with a MAF of at least 0.05 and maximum correlation of 0.1 in the OncoArray dataset, using purpose-written software (http://ccge.medschl.cam.ac.uk/software/pccalc). A similar approach was used for the iCOGS dataset.

Breast cancer and epithelial ovarian cancer PRS

PRSs were constructed as the weighted sum of alleles for 313 SNPs for breast cancer and 30 SNPs for epithelial ovarian cancer (EOC), thus the PRS for each participant, *i*, was calculated as:

$$PRS_i = \sum_{j=1}^{N} \beta_j g_{ij}$$

where g_{ij} is the genotype or imputed dosage for variant *j* observed for individual *i* and β_j is

weight for the j^{th} SNP.

The weights for the breast cancer PRS were the log Odds Ratio (log-OR) estimates of association used to construct the 313 SNP PRS based on data from the general population and reported by Mavaddat et al[8]. The weights used to construct the PRS for overall breast cancer (denoted as PRS_{BC}), ER-negative breast cancer (PRS_{ER-}) or ER-positive breast cancer (PRS_{ER+}) are shown in Supplementary Table 1).

Two PRS for epithelial ovarian cancer (EOC) were constructed:

1. A PRS for invasive EOC (PRS_{EOC}) based on 30 SNPs which were: (i) associated with EOC; or (ii) identified through pleiotropic GWAS of breast, EOC and prostate cancer[3,9] at genome-wide significance levels in the combined analyses of the three cancers, but also showed consistent associations with EOC in the Phelan et al[3].
2. A PRS for high grade serous (HGS) ovarian cancer. As HGS is the predominant subtype observed in *BRCA1* and *BRCA2* pathogenic variant carriers[10] a 22 SNP high-grade serous EOC PRS (PRS_{HGS}) was constructed. This PRS was restricted to SNPs that exhibited associations at genome-wide significance level ($P<5x10^{-8}$) with any EOC histotype, was nominally associated ($P<0.05$) with HGS EOC, and the direction of the association for HGS EOC was consistent with the EOC association[3].

The SNPs and the corresponding log-OR weights used in the PRS_{EOC} and PRS_{HGS} are shown in Supplementary Table 2.

Calculating the theoretical PRS

The theoretical PRS distribution under a multiplicative model was used in comparisons against the PRS percentile specific association estimates. For the theoretical PRS, the variance attributable to SNP *i* was given by:

$$V_i = (1-p_i)^2 E_i^2 + 2p_i(1-p_i)(\beta_i - E_i)^2 + p_i^2(2\beta - E_i)^2$$

where E_i is the expected value of β, given by:

$$E_i = 2p_i(1-p_i)\beta_i + 2p_i^2\beta_i$$

where β_i is the per-allele log-OR and p_i is the allele frequency for SNP i[11] and were obtained from the population-data used in the PRS construction for breast and ovarian cancer (Tables S1 and S2)[3,8]. The mean PRS is then given by:

$$\overline{PRS} = \sum_{i=1}^{N} E_i$$

and the theoretical PRS variance is given by:

$$V = \sum_{i=1}^{N} V_i$$

The allele frequencies were obtained from the 1000 Genomes Project European ancestry samples. The theoretical HRs at each percentile were calculated assuming the PRS is normally distributed with mean $\overline{PRS}$ and variance V (i.e. the HRs were log-normally distributed).

Description of statistical models

Weighted cohort analysis

The retrospective cohort association analyses were undertaken using weighted Cox regression models[12]. These analyses accounted for the non-random sampling of *BRCA1* and *BRCA2* carriers with respect to their disease (breast cancer and ovarian cancer) status. In such retrospective studies, affected carriers tend to be oversampled because *BRCA1* and *BRCA2* testing is targeted to affected individuals who may also be diagnosed at an early age. Therefore, the carriers in CIMBA retrospective study do not represent a true cohort of *BRCA1* and *BRCA2* carriers. We have previously shown that under these conditions, standard Cox regression analysis leads to biased estimates of the rate ratios[12,13]. To correct for this bias, we used the weighted cohort approach[12,13]. Briefly, this method involves assigning different weights to cancer cases and unaffected individuals which are age- and gene-specific, such that the weighted observed incidence rates are consistent with established incidence rates for carriers of pathogenic variants in *BRCA1* and *BRCA2*[14]. This

approach has been shown in simulation studies to yield unbiased estimates of association[12,13]. The weighted cohort analysis was carried out in R "survival" library command `coxph(model,robust=TRUE,weights=w)` where w represents the age specific weights.

Model comparisons

Likelihood ratio tests (LRTs) were undertaken to determine whether the models which include interaction terms (age-varying PRS, PRS interaction with gene variant location and PRS interaction with gene variant class) fitted data better than the nested model that did not include the interaction term. Here we considered two models: (i) a model that includes the PRS interaction term, with a corresponding log-likelihood, L_I and the nested model without the interaction term with log-likelihood L_N. Hence, the LRT comparing these models has the form:

$$-2[L_N - L_I] \sim \chi^2_{\Delta d}$$

where Δd denotes degrees of freedom, given by the difference in number of parameters estimated between the two models.

BRCA1 and _BRCA2_ Cohort Consortium (BBCC) prospective cohort

The BBCC included data from the International *BRCA1/2* Carrier Cohort Study (IBCCS), Breast Cancer Family Registry (BCFR) and the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) IBCCS study participants were recruited between 1997 and 2011 from 18 European cancer genetics centres and Quebec, Canada. Most women were recruited through large national studies in the United Kingdom, Netherlands and France. All centres actively followed participants through questionnaires. Additionally, where possible, passive follow-up by pathology (Denmark and Netherlands), cancer and death registry linkage (Denmark, Netherlands, Sweden and the United Kingdom), and validation of self-reported cancer diagnoses and preventive surgeries

through medical records.

The BCFR is a family cohort recruited from six sites from Australia, Canada and the USA. The families were followed-up regularly by annual contact of probands and systematic 5-year follow-up of families that collected demographic and epidemiological data from all study participants.

The kConFab recruited pathogenic variant carriers from multi-case families that had been ascertained since 1997 by family cancer clinics in Australia and New Zealand. kConFab study participants were independent from BCFR participants from Australia. Study participants were systematically followed by the kConFab Follow-Up Study[15] using mailed questionnaires every three years, with self-reported cancers and prophylactic surgeries confirmed from medical records. BBCC follow-up ended in December 2013[16].

Association analysis in prospective cohorts

To assess associations between the PRS and breast cancer risk, eligibility was restricted to female *BRCA1* and *BRCA2* carriers who at completion of the baseline questionnaire were free of any cancer diagnosis (excluding non-melanoma skin cancer) and had not undergone risk-reducing bilateral mastectomy. Study participants were followed from baseline until the first of: (i) age 80-years; (ii) death; (iii) completion of last follow-up questionnaire or last record linkage, whichever occurred last; (iv) risk-reducing bilateral mastectomy; or (v) diagnosis of any first cancer (apart from non-melanoma skin cancer). Participants diagnosed with a first breast cancer were considered affected.

To assess associations between the PRS and ovarian cancer risk, eligibility was restricted to women who had not been diagnosed with ovarian cancer and had not had RRSO at the time of baseline questionnaire completion. To maximise statistical power, carriers with a prior breast cancer or non-melanoma skin cancer diagnosis were retained for the prospective ovarian cancer analyses, but carriers with prior diagnoses of other cancers were excluded, in line with previous prospective studies of ovarian cancer risk for *BRCA1/2* pathogenic variant carriers[16]. Participants were followed from baseline until the first of: (i)

age 80-years; (ii) death; (iii) completion of last follow-up questionnaire or record linkage, whichever happened last; (iv) bilateral RRSO, or bilateral salpingectomy, or removal of both ovaries for any other reason; or (v) any cancer diagnosis (except breast or non-melanoma skin cancer). Carriers diagnosed with invasive ovarian, fallopian tube, or peritoneal cancer during the follow-up were considered affected.

Associations using the harmonised prospective cohorts were analysed using Cox regression, separately for *BRCA1* and *BRCA2* carriers. Statistical models were stratified by consortia (CIMBA or BBCC), birth cohort, country, and Ashkenazi Jewish ancestry, adjusted for family history of the appropriate cancer in first- and second-degree relatives. Robust variance estimates were calculated considering family membership.

Calculating absolute cancer risks by PRS

Breast cancer absolute risks were calculated by PRS category and also by PRS category in combination with variant locations in *BRCA1* and *BRCA2*, and in combination with family history of breast cancer (absence or presence of family history).

For these calculations we assumed external estimates of overall breast cancer incidence and breast cancer incidence estimates for different pathogenic variant locations and cancer family history status. The external estimates were obtained from previously published prospective penetrance studies in *BRCA1* and *BRCA2* pathogenic variant carriers[16]. For all analyses, to obtain the breast cancer incidences for each PRS percentile category, we constrained the breast cancer incidences over all PRS categories to agree with the prospectively estimated breast cancer incidence rates using the constraining approach described previously[8,16-18]. In this we assume that the breast cancer incidence for someone in PRS category c is given by $\lambda_0(t)\exp(\beta_c)$ where $\lambda_0(t)$ is the baseline incidence (for those in the baseline PRS category) which is unknown, and β_c is the corresponding log-HR of association with breast cancer risk for a carrier in category *c* relative to the baseline category. Given this constraining, it was previously shown[16,17] that $\lambda_0(t)$ is given by:

$$\lambda_0(t) \;=\; i(t)\frac{\sum_c \tau_c S_c(t-1)}{\sum_c \tau_c \exp(\beta_c) S_c(t-1)}$$

where $i(t)$ is the assumed external incidence (i.e. the average over all PRS effects), τ_c is the proportion of carriers in PRS category c and $S_c(t)$ is the probability of surviving the disease to age t in PRS category c. $\lambda_0(t)$ can be calculated iteratively assuming $S_c(0)=1$ over the ages t. Once $\lambda_0(t)$ was calculated, the incidence for each PRS category is given by: $\lambda_0(t)\exp(\beta_c)$. This process was carried out assuming the external incidence estimates for overall breast cancer, incidences by pathogenic variant location or by family history separately[16].

Calculating 10-year cancer risks

The 10-year risk of developing breast or ovarian cancer at age t was calculated as the risk difference between ages (t+10) and t, conditional on not developing cancer up to age t. Mathematically this can be written as:

$$R(t)_{10} = \frac{P(t+10) - P(t)}{1 - P(t)}$$

where $R(t)_{10}$ is the 10-year risk and $P(t)$ is the cumulative disease risk at age t and is calculated using the PRS specific incidences calculated in the previous section.

Supplementary Results

Absolute risks by PRS, variant location and family history (results)

Carriers of pathogenic variants in the non-central gene regions had greater risk of developing breast cancer (5th-95th PRS percentiles *BRCA1* 5' end 61%-88%, 3' end 60%-91%; *BRCA2* (narrow) 5' end 62%-87%, 3' end 60%-92%; *BRCA2* (wide) 5' end 67%-91%, 3' end 61%-93%) compared to carriers with variants in the central regions (*BRCA1* 49%-75%; *BRCA2* (narrow) 42%-73%; *BRCA2* (wide) 41%-71%) (Table S5; Figures S5-S7).

Carriers with a family history of breast cancer (at least one affected first or second degree relative) had larger absolute risks of developing breast cancer up to age 80-years (*BRCA1* 65%-88%; *BRCA2* 62%-85%) compared with carriers without a family history of breast cancer (*BRCA1* 46%-71%; *BRCA2* 62%-85%) (Table S5; Figures S8-S9).

Detailed breast and ovarian cancer absolute risks by PRS percentiles (results)

Table S6 illustrates the absolute risks by age 80-years of developing breast cancer and ovarian cancer for pathogenic variant carriers. These absolute risks are presented for the PRS deciles as well as the most extreme first (i.e. 1st and 99th) and fifth (i.e. 5th and 95th) PRS percentiles. The PRS_{ER-} is presented for *BRCA1* carriers with respect to their breast cancer risk, whilst the PRS_{BC} is shown for *BRCA2* carrier breast cancer risk. The PRS_{HGS} is presented for both *BRCA1* and *BRCA2* carriers with respect to ovarian cancer risks.

Statistical software (R and Stata) commands used for statistical analyses

R Cox regression

```
library(survival)
coxph(Surv(CENSORING.AGE, CENSORING.STATUS) ~ strata(STRATA) +
cluster(FAMILY) + BIRTH.COHORT + PRINCIPAL.COMPONENTS +
NORMALISED.PRS, robust = TRUE, weights = WEIGHTS, data=DATA)
```

Stata age-varying PRS analysis

```
stset CENSORINGAGE [pweight = WEIGHTS], id(ID) f(CENSORINGSTATUS)
xi: stcox NORMALISEDPRS i.BIRTHCOHORT PRINCIPALCOMPONENTS*, ///
strata(STRATA) cluster(FAMILY) tvc(NORMALISEDPRS)
// PRINCIPALCOMPONENTS* represents all principal components
```

Stata: C-index for discrimination

```
net from http://www.homepages.ucl.ac.uk/~rmjwiww/stata/epi
net install cindex
* Fit appropriate Cox model and obtain linear predictions
stcox ...
predict LINPRED, xb
set seed 25456
bootstrap c = r(C_adj_correct2), cluster(FAMILY) reps(1000): cindex
LINPRED, ///
strata(STRATA) adj(_IBIRTHCOHORT* PRINCIPALCOMPONENTS*)
// PRINCIPALCOMPONENTS* represents all principal components
// _IBIRTHCOHORT* represents all birth cohorts (created internally
from the "BIRTHCOHORT" variable by Stata after fitting the -stcox-
model)
```

SUPPLEMENTARY TABLE LEGENDS

Table S1

The 313 SNPs used to construct the breast cancer PRS[8]. The same set of 313 SNPs was used to construct the PRS_{ER-} and PRS_{ER+}. The ER-specific PRS used different SNP weights (log-ORs for ER-specific breast cancer) if they had a statistically significant different effect on ER-subtype from a population-based breast cancer case-only analysis.

Table S2

The 30 SNPs used to construct the ovarian cancer PRS. The 22 SNPs used to form the high-grade serous ovarian cancer PRS are highlighted in grey. The high-grade serous specific PRS was limited to SNPs that showed genome-wide statistical significance ($P<5x10^{-8}$) with any of the ten ovarian cancer subtypes, had concordant direction of effects between overall all invasive and high-grade serous disease, and exhibited nominal statistical significance ($P<0.05$) with high-grade serous ovarian cancer[3]. The "overall" and "high-grade serous" ovarian cancer (per-allele) effect sizes and P-values were taken from[3] and/or[9].

Table S3

Retrospective cohort characteristics for 18,935 *BRCA1* and 12,339 *BRCA2* carriers recruited by the CIMBA. Breast cancer and ovarian cancer refer to the first cancer diagnosis. Censoring ages are reported in years. Pathogenic variant classes: I = unstable or no protein; II = stable mutant protein; III = consequence unknown. Pathogenic variant locations are in base pairs (bp) within the *BRCA1* and *BRCA2* genes. ER-status is oestrogen receptor status of the breast tumour. Cancer family history is reported for the relevant cancer from first and second degree relatives. "Unknown" family history = reported unknown cancer family history, "missing" family history = family history data not collected. IQR = interquartile range; SD = standard deviation.

Table S4

Validation data summary statistics from prospective cohorts (CIMBA and BBCC). Validation data are presented for the breast cancer PRS and ovarian cancer PRS by disease status at censoring. The PRS_{ER-} is reported for *BRCA1* carriers, whilst the PRS_{ER+} is presented for *BRCA2* carriers with respect to the breast cancer data. PRS_{HGS} is shown for both *BRCA1* and *BRCA2* carriers for the ovarian cancer data. The median (IQR) age at start of follow-up, follow-up time and age at cancer diagnosis (years) are displayed. The mean and SD are shown for the appropriate PRS. IQR = interquartile range; N = sample size; SD = standard deviation.

Table S5

Assumed proportions and hazard ratios used to constrain the breast cancer incidences from the external BBCC prospective cohort study for breast cancer family history and gene variant location[16]. The absolute risks of breast cancer at the 5th, 50th and 95th percentiles of the PRS are shown (absolute risk curves are plotted in Figures S5-S9).

Table S6

Absolute breast cancer and ovarian cancer risks by age 80-years for *BRCA1* and *BRCA2* carriers for different PRS percentiles. The reported PRS percentiles are: (i) PRS_{ER-} for *BRCA1* carrier breast cancer; (ii) PRS_{BC} for *BRCA2* carrier breast cancer; (iii) PRS_{HGS} for *BRCA1* carrier ovarian cancer; and (iv) PRS_{HGS} for *BRCA2* carrier ovarian cancer.

SUPPLEMENTARY FIGURE LEGENDS

Figure S1

Histograms of imputation accuracy (r^2 statistics) for the 313 breast cancer PRS SNPs. Imputations were performed separately for genotyping arrays (iCOGS or OncoArray) and separately for *BRCA1* and *BRCA2* carriers. All SNPs were well imputed ($r^2 \geq 0.49$).

Figure S2

Histograms of imputation accuracy (r^2 statistics) for the 30 ovarian cancer PRS SNPs. Imputations were performed separately for genotyping arrays (iCOGS or OncoArray) and separately for *BRCA1* and *BRCA2* carriers. All SNPs were well imputed ($r^2 \geq 0.64$).

Figure S3

Forest plots of country specific PRS hazard ratios estimated using the CIMBA retrospective cohort. These models tested for heterogeneity in PRS effects across countries by fitting a PRS by country interaction term. The baseline country was assumed to be UK/Eire. Heterogeneity was assessed using a likelihood ratio test, comparing the model that included the interaction term to a nested model that did not include the interaction term. (A) PRS_{ER-} was used for *BRCA1* carriers ($P_{het}=0.26$). (B) PRS_{BC} was used for *BRCA2* carriers ($P_{het}=0.58$). (C) PRS_{HGS} used for *BRCA1* carriers ($P_{het}=0.08$). (D) PRS_{HGS} used for *BRCA2* carriers ($P_{het}=0.95$).

Figure S4

Estimated 10-year risks of developing breast cancer and ovarian cancer by different PRS distribution percentiles.

Figure S5

Predicted age-specific absolute risks of developing breast cancer by PRS_{ER-} percentiles and by *BRCA1* variant location. Risks were calculated assuming the retrospective cohort HR

estimates (Table 2). (A) Predicted absolute risks of developing breast cancer for *BRCA1* carriers with a variant in the 5' to c.2281 region. (B) Predicted absolute risks of developing breast cancer for *BRCA1* carriers with a variant in the c.2282 to c.4071 region. (C) Predicted absolute risks of developing breast cancer for *BRCA1* carriers with a variant in the c.4072 to 3' region.

Figure S6

Predicted age-specific absolute risks of developing breast cancer by PRS_{BC} percentiles and by *BRCA2* variant location (narrow definition). Risks were calculated assuming the retrospective cohort HR estimates (Table 2). (A) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the 5' to c.3846 region. (B) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the c.3847 to c.6275 region. (C) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the c.6276 to 5' region.

Figure S7

Predicted age-specific absolute risks of developing breast cancer by PRS_{BC} percentiles and by *BRCA2* variant location (wide definition). Risks were calculated assuming the retrospective cohort HR estimates (Table 2). (A) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the 5' to c.2830 region. (B) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the c.2831 to c.6402 region. (C) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with a variant in the c.6403 to 5' region.

Figure S8

BRCA1 carriers*:* Predicted age-specific absolute risks of developing breast cancer by PRS_{ER-} percentiles and by family history (FH) of breast cancer. Risks were calculated assuming the retrospective cohort HR estimates (Table 2). (A) Predicted absolute risks of

developing breast cancer for *BRCA1* carriers with no family history of breast cancer. (B) Predicted absolute risks of developing breast cancer for *BRCA1* carriers with positive family history of breast cancer.

Figure S9

BRCA2 carriers: Predicted age-specific absolute risks of developing breast cancer by PRS_{BC} percentiles and by family history (FH) of breast cancer. Risks were calculated assuming the retrospective cohort HR estimates (Table 2). (A) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with no family history of breast cancer. (B) Predicted absolute risks of developing breast cancer for *BRCA2* carriers with positive family history of breast cancer.

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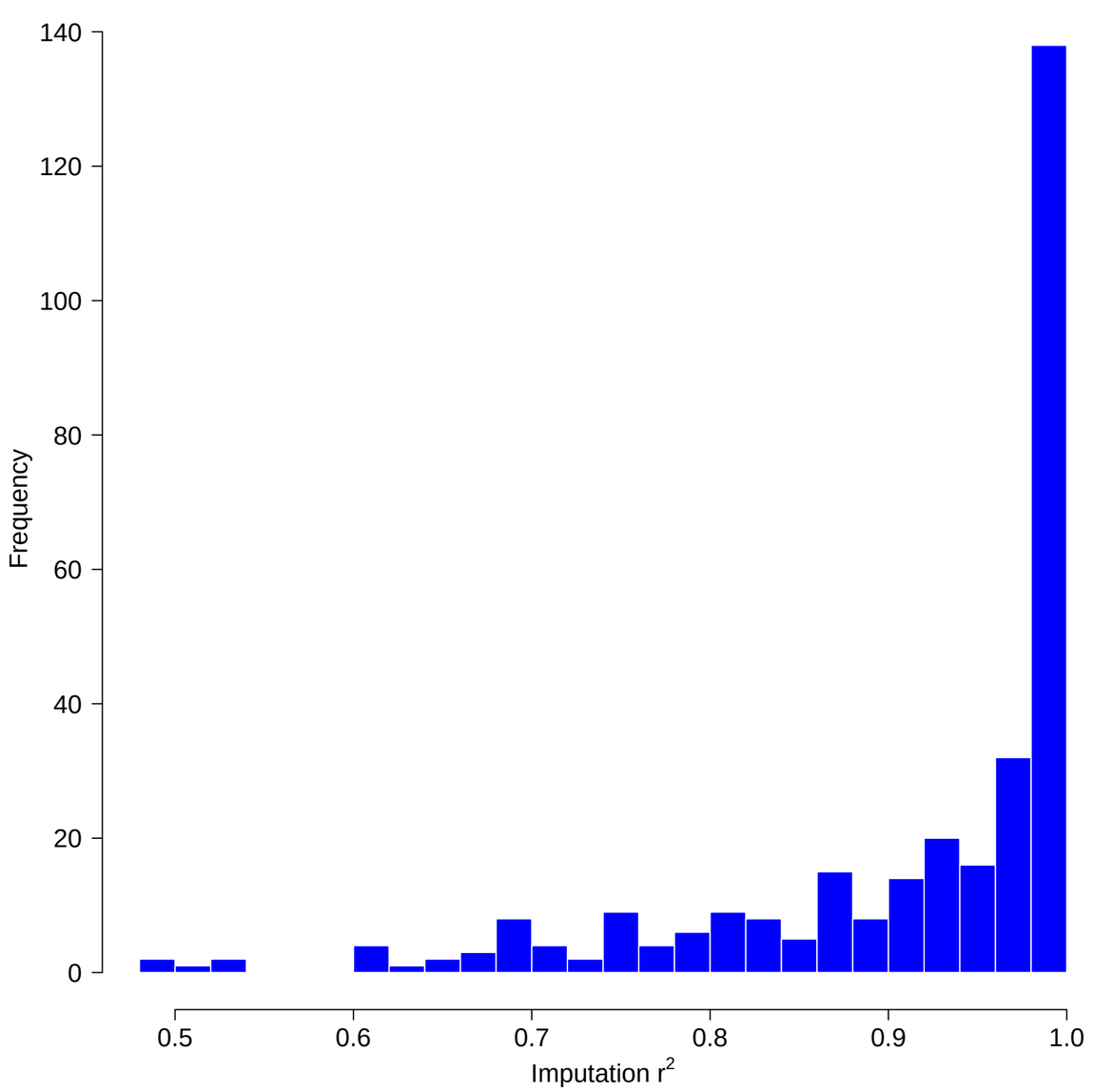
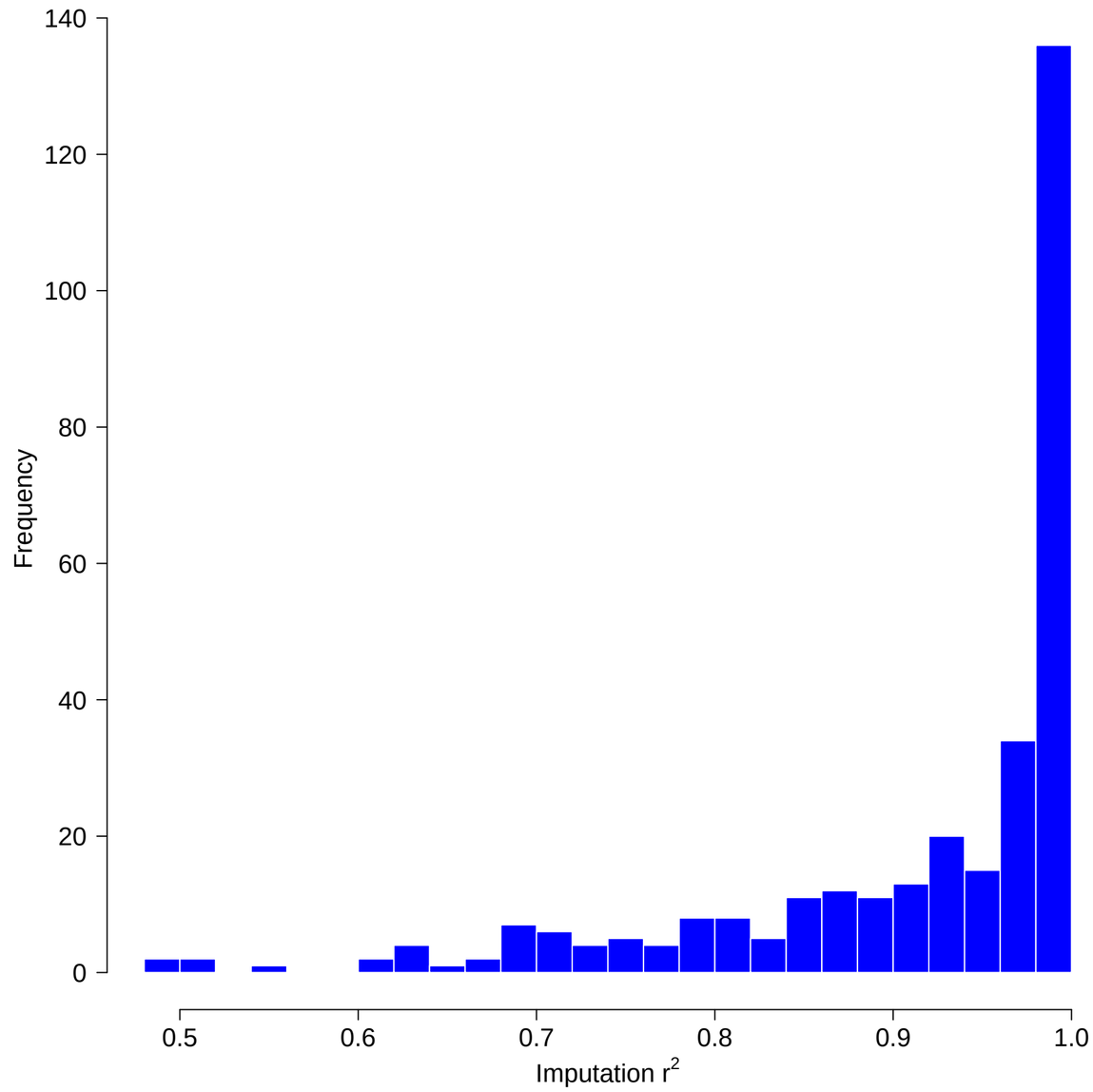
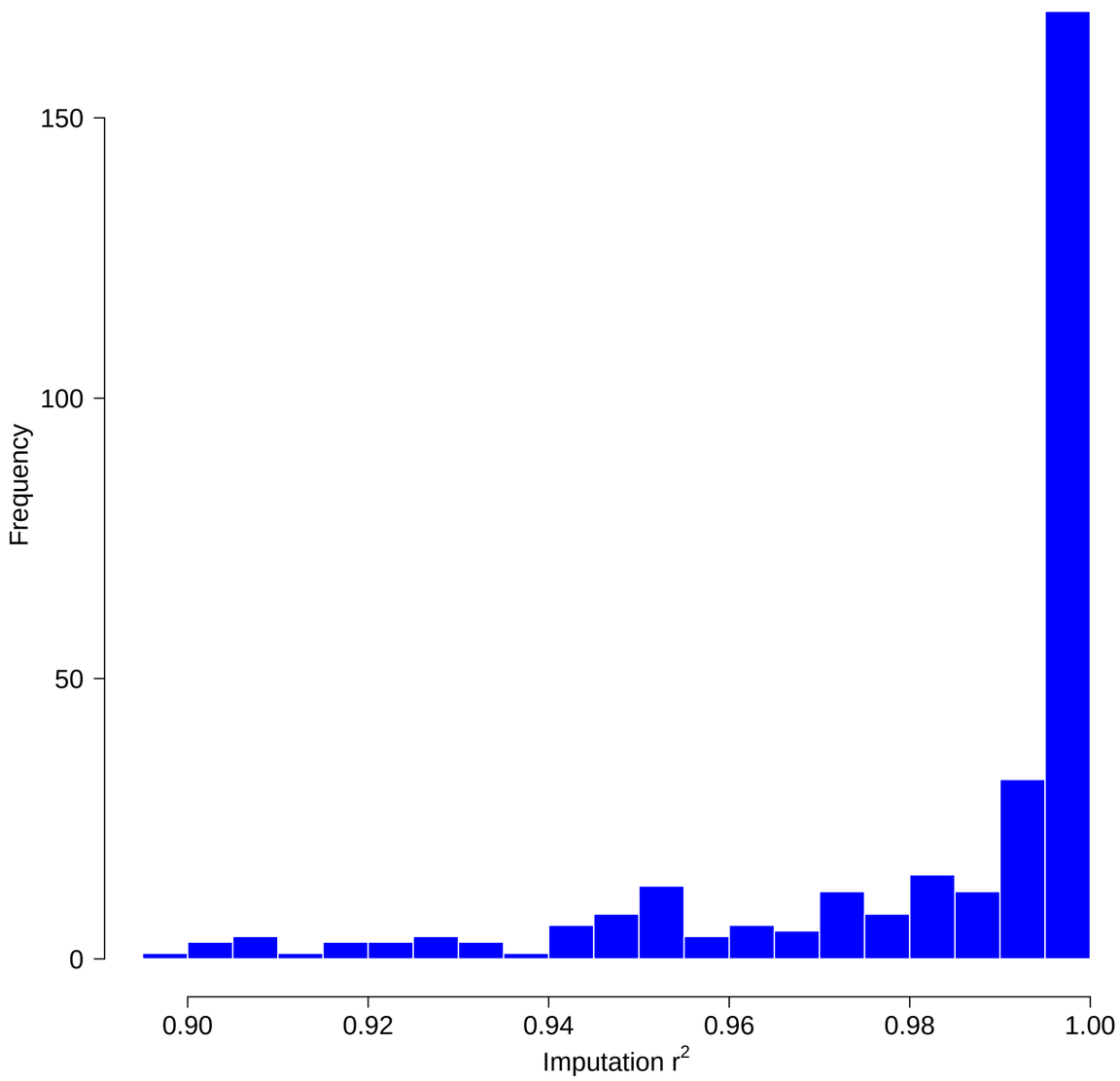
Figure S1


(A) iCOGS: BRCA1 carriers
Frequency
0
20
40
60
80
100
120
140
0.5
0.6
0.7
0.8
0.9
1.0
Imputation r2


(B) iCOGS: BRCA2 carriers
Frequency
0
20
40
60
80
100
120
140
0.5
0.6
0.7
0.8
0.9
1.0
Imputation r2


(C) OncoArray: BRCA1 carriers
Frequency
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50
100
150
0.90
0.92
0.94
0.96
0.98
1.00
Imputation r2

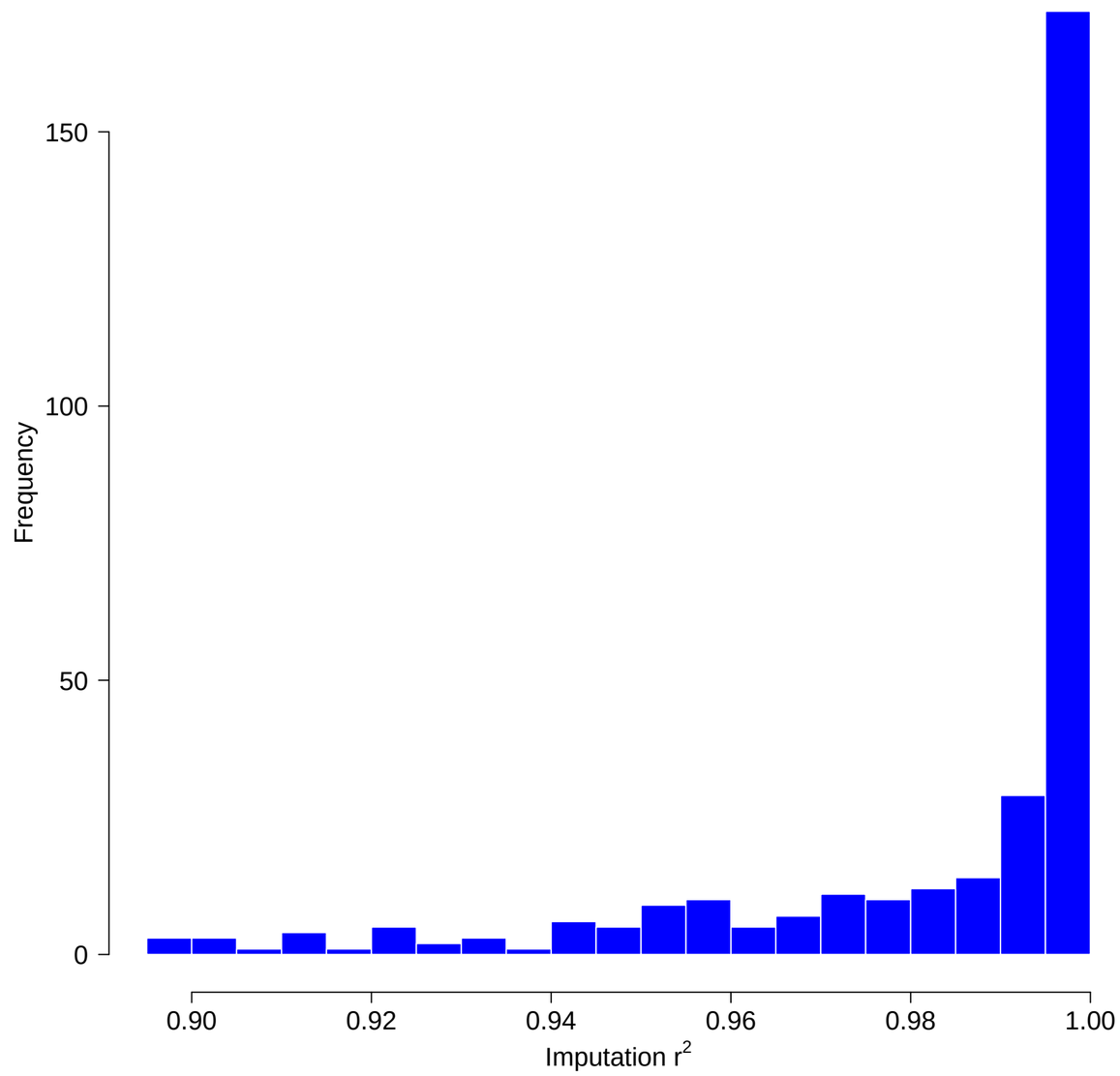
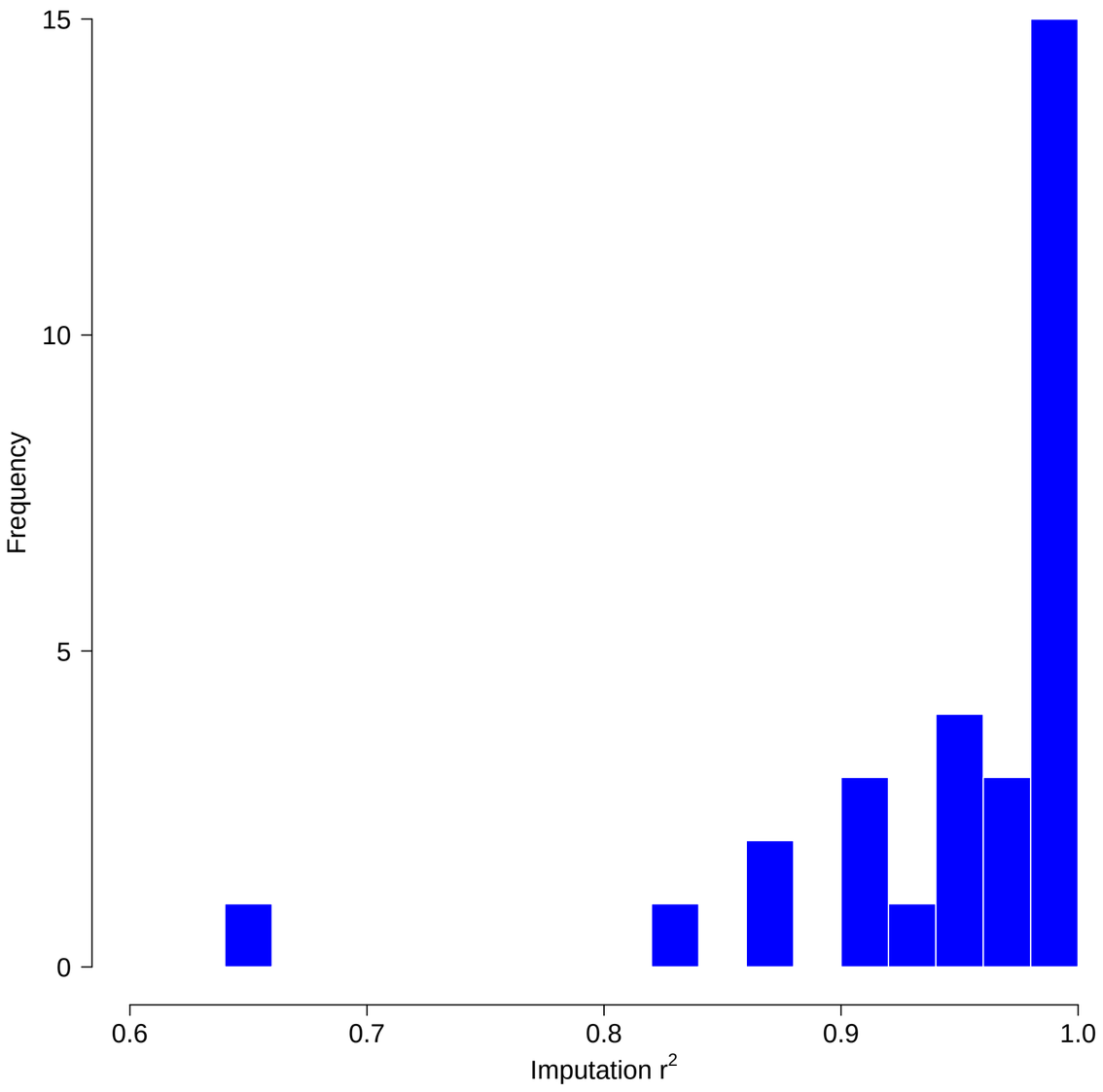
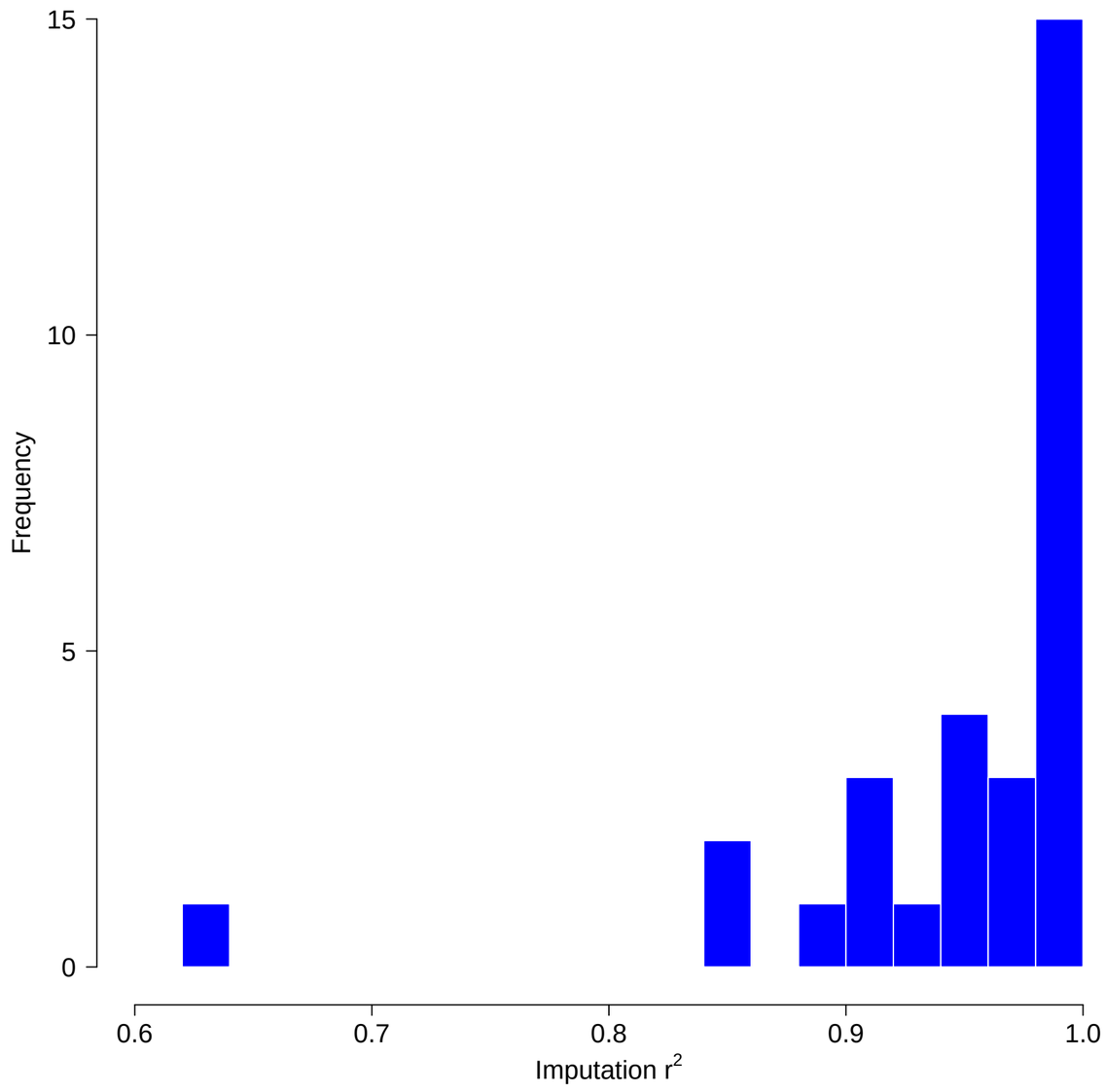
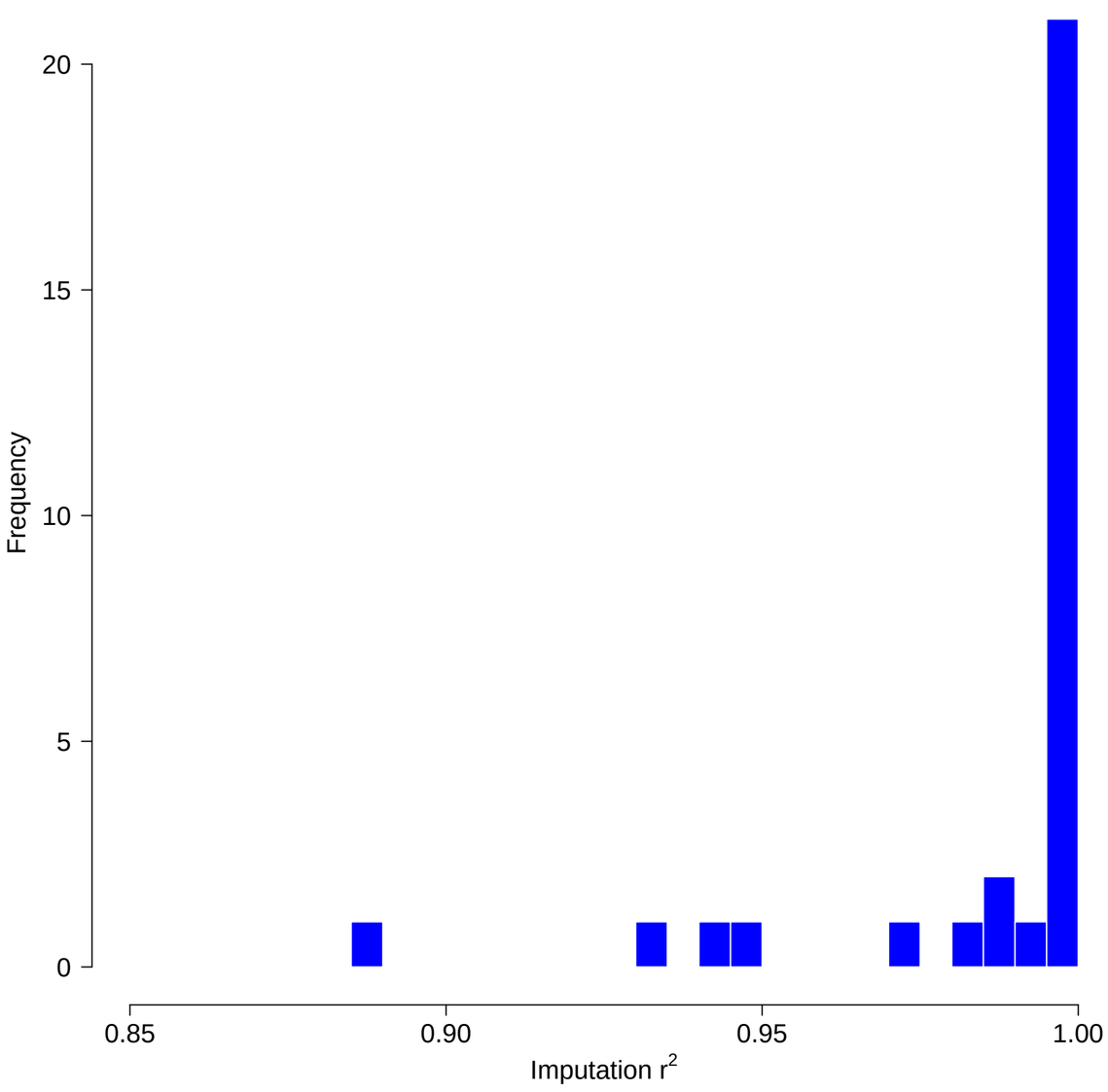

(D) OncoArray: BRCA2 carriers
Frequency
0
50
100
150
0.90
0.92
0.94
0.96
0.98
1.00
Imputation r2

Figure S2


(A) iCOGS: BRCA1 carriers
Frequency
0
5
10
15
0.6
0.7
0.8
0.9
1.0
Imputation r2


(B) iCOGS: BRCA2 carriers
Frequency
0
5
10
15
0.6
0.7
0.8
0.9
1.0
Imputation r2


(C) OncoArray: BRCA1 carriers
Frequency
0
5
10
15
20
0.85
0.90
0.95
1.00
Imputation r2

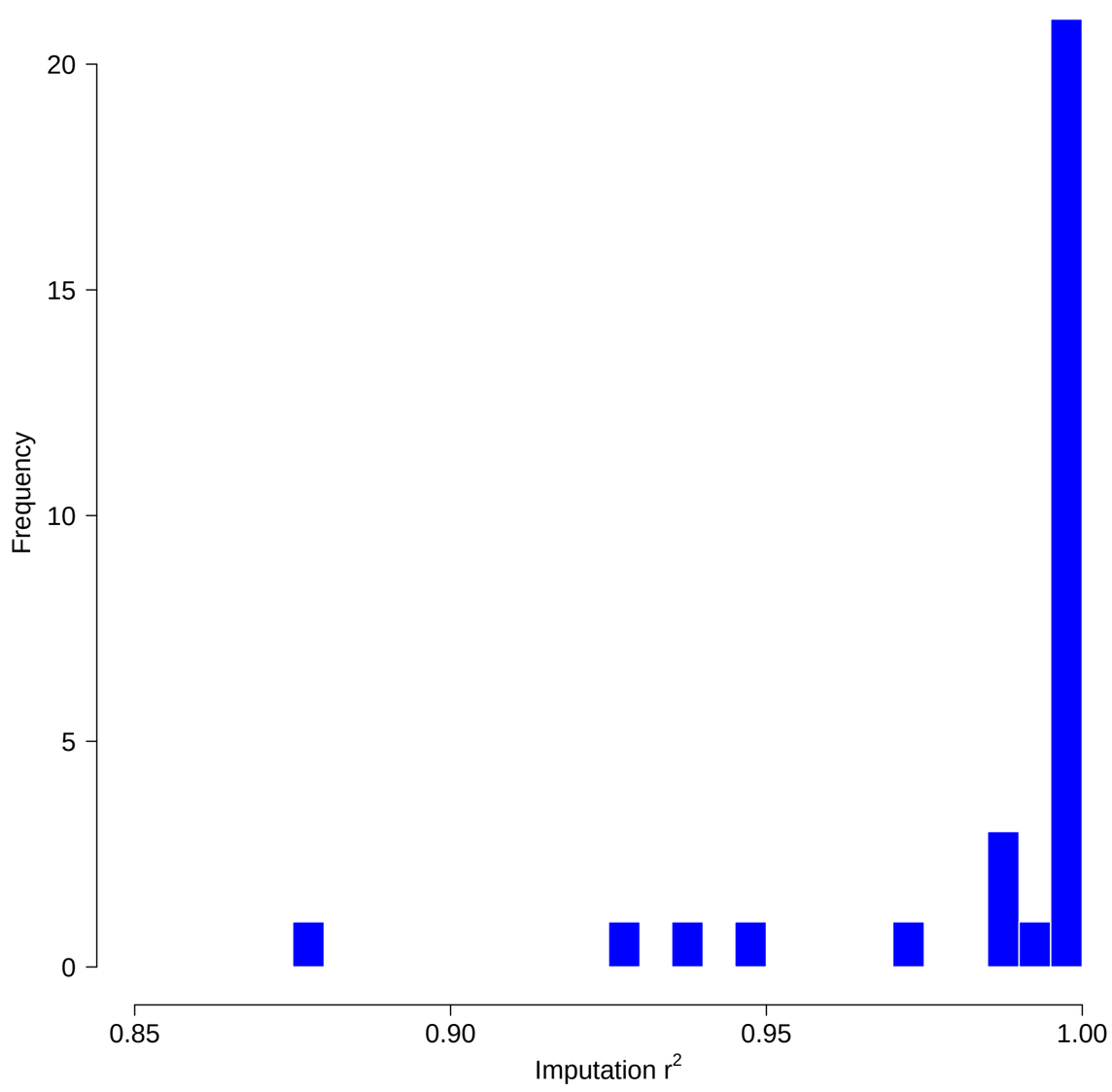

(D) OncoArray: BRCA2 carriers
Frequency
0
5
10
15
20
0.85
0.90
0.95
1.00
Imputation r2

Figure S3

(A) BRCA1 carriers: ER−negative PRS

Country	Unaffected	Affected	HR (95% CI)
UK/EIRE	971	822	1.21 (1.11−1.32)
AUSTRALIA	504	525	1.33 (1.17−1.51)
AUSTRIA	277	279	1.29 (1.09−1.53)
BELGIUM	160	163	1.29 (0.98−1.71)
CANADA	363	280	1.22 (1.07−1.39)
CZECH REPUBLIC	68	106	1.59 (1.19−2.12)
DENMARK	556	332	1.25 (1.12−1.41)
FINLAND	71	58	0.97 (0.72−1.29)
FRANCE	666	859	1.27 (1.14−1.41)
GERMANY	749	1316	1.47 (1.33−1.62)
GREECE	97	152	1.47 (1.15−1.88)
HUNGARY	101	179	1.46 (1.14−1.88)
ISRAEL	157	106	1.38 (1.15−1.65)
ITALY	624	673	1.28 (1.16−1.43)
LATVIA	14	30	0.82 (0.52−1.28)
LITHUANIA	135	89	1.15 (0.95−1.41)
NETHERLANDS	663	539	1.37 (1.22−1.55)
POLAND	400	300	1.33 (1.19−1.50)
PORTUGAL	80	38	1.66 (1.31−2.10)
RUSSIA	25	49	1.27 (0.91−1.76)
SOUTH AFRICA	23	38	1.17 (0.74−1.83)
SPAIN	424	399	1.28 (1.12−1.45)
SWEDEN	290	227	1.07 (0.92−1.24)
USA	2044	1914	1.27 (1.19−1.35)
Main analysis	**9462**	**9473**	**1.29 (1.25−1.32)**

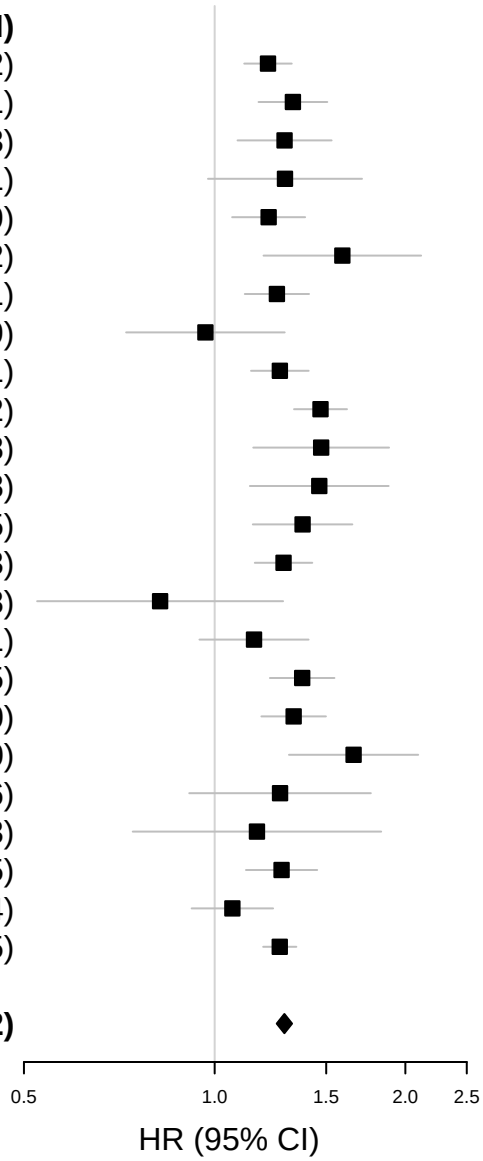


Figure S3

(B) BRCA2 carriers: Overall PRS

Country	Unaffected	Affected	HR (95% CI)
UK/EIRE	897	785	1.42 (1.29−1.55)
AUSTRALIA	433	416	1.32 (1.13−1.54)
AUSTRIA	124	147	1.03 (0.82−1.28)
BELGIUM	87	76	1.34 (1.02−1.74)
CANADA	202	179	1.46 (1.21−1.75)
DENMARK	339	250	1.41 (1.20−1.66)
FINLAND	65	68	1.54 (1.16−2.06)
FRANCE	395	724	1.37 (1.19−1.56)
GERMANY	447	712	1.20 (1.06−1.36)
HUNGARY	48	65	1.44 (0.94−2.19)
ICELAND	28	114	1.01 (0.69−1.47)
ISRAEL	168	106	1.29 (1.03−1.63)
ITALY	246	432	1.31 (1.10−1.55)
NETHERLANDS	469	255	1.30 (1.13−1.49)
PORTUGAL	73	88	1.22 (0.89−1.69)
SOUTH AFRICA	54	92	1.34 (0.93−1.94)
SPAIN	479	508	1.20 (1.06−1.35)
SWEDEN	41	30	1.88 (1.21−2.94)
USA	1397	1248	1.27 (1.18−1.37)
Main analysis	**5992**	**6295**	**1.30 (1.26−1.35)**

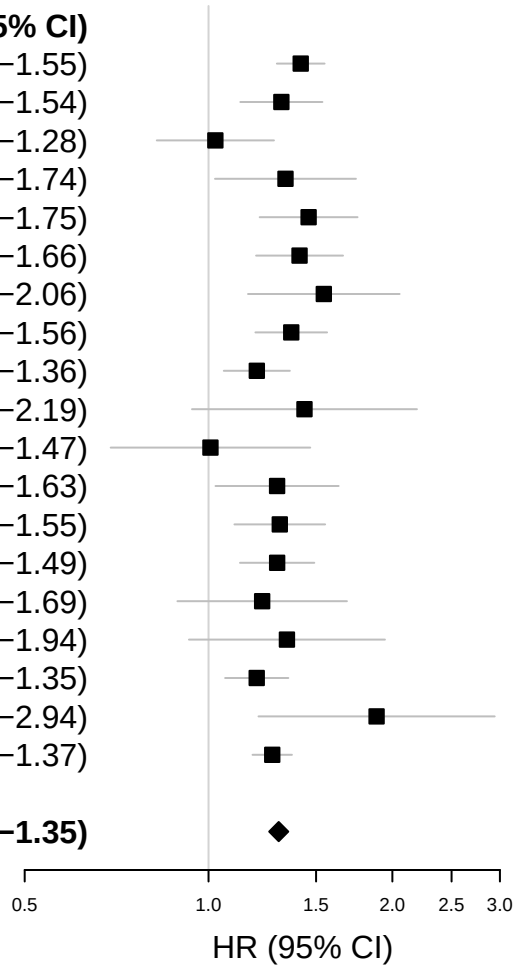


Figure S3

(C) BRCA1 carriers: HGS PRS

Country	Unaffected	Affected	HR (95% CI)
UK/EIRE	1621	172	1.27 (1.06−1.54)
AUSTRALIA	952	77	1.48 (1.16−1.90)
AUSTRIA	509	47	1.63 (1.25−2.13)
BELGIUM	298	25	1.08 (0.68−1.70)
CANADA	574	69	1.26 (0.98−1.61)
CZECH REPUBLIC	142	32	2.36 (1.32−4.24)
DENMARK	770	118	1.52 (1.21−1.92)
FINLAND	114	15	1.25 (0.68−2.31)
FRANCE	1347	178	1.41 (1.15−1.74)
GERMANY	1885	180	1.51 (1.22−1.86)
GREECE	198	51	2.66 (1.95−3.63)
HUNGARY	251	29	0.78 (0.43−1.42)
ISRAEL	225	38	1.05 (0.60−1.84)
ITALY	1045	252	1.26 (0.99−1.60)
LATVIA	32	12	1.73 (0.81−3.71)
LITHUANIA	151	73	1.20 (0.79−1.82)
NETHERLANDS	1112	90	1.27 (1.06−1.52)
POLAND	663	37	1.35 (1.09−1.67)
PORTUGAL	103	15	1.27 (0.75−2.13)
RUSSIA	57	17	1.85 (0.75−4.57)
SOUTH AFRICA	56	5	0.65 (0.31−1.38)
SPAIN	721	102	1.12 (0.87−1.45)
SWEDEN	432	85	1.49 (1.10−2.00)
USA	3609	349	1.24 (1.10−1.40)
Main analysis	**16867**	**2068**	**1.33 (1.26−1.41)**

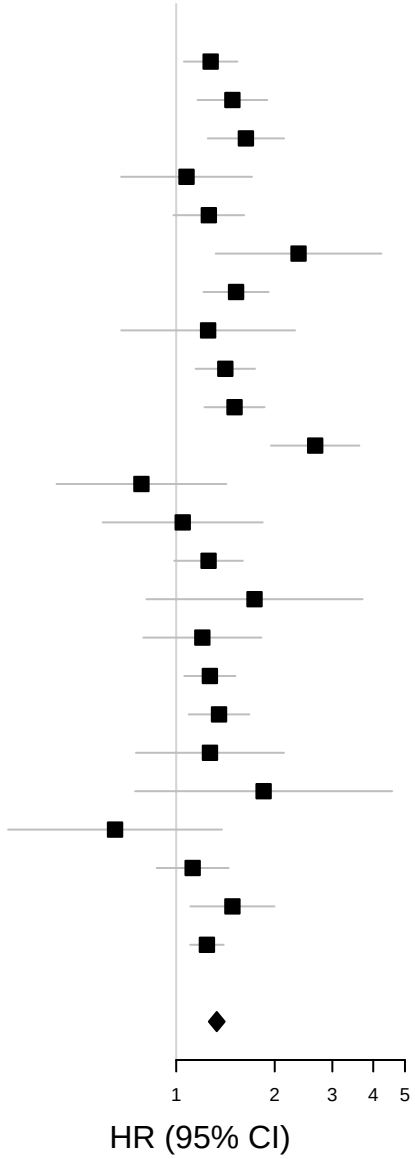


Figure S3

(D) BRCA2 carriers: HGS PRS

Country	Unaffected	Affected	HR (95% CI)
UK/EIRE	1579	103	1.63 (1.27−2.09)
AUSTRALIA	820	29	1.19 (0.89−1.60)
AUSTRIA	262	9	2.25 (1.30−3.87)
BELGIUM/NETHERLANDS	852	35	1.07 (0.77−1.48)
CANADA	355	26	1.52 (0.98−2.37)
DENMARK/ICELAND	687	44	1.47 (1.02−2.13)
FINLAND/LITHUANIA/RUSSIA	145	8	1.00 (0.36−2.78)
FRANCE	1053	66	1.64 (1.09−2.48)
GERMANY	1094	65	1.34 (0.92−1.95)
GREECE/ITALY	653	57	1.29 (0.80−2.07)
HUNGARY	105	8	2.39 (0.86−6.63)
ISRAEL	257	17	0.96 (0.56−1.66)
PORTUGAL/SPAIN	1087	61	1.31 (0.94−1.82)
SOUTH AFRICA	134	12	0.92 (0.14−6.07)
SWEDEN	61	10	1.70 (0.78−3.68)
USA	2477	168	1.52 (1.24−1.86)
Main analysis	**16867**	**2068**	**1.42 (1.28−1.57)**

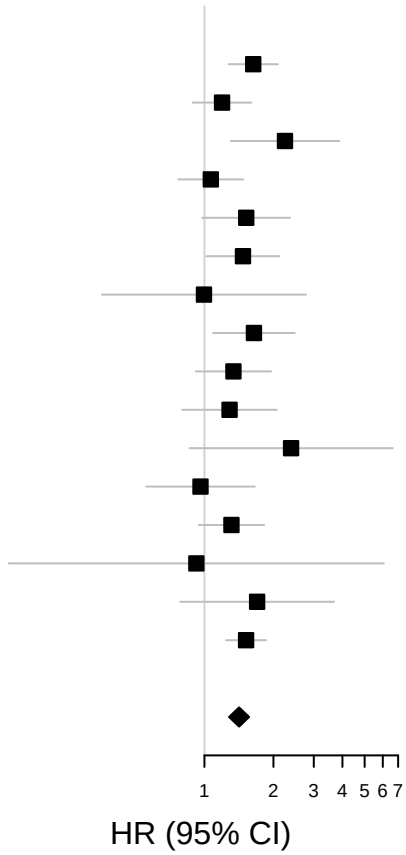
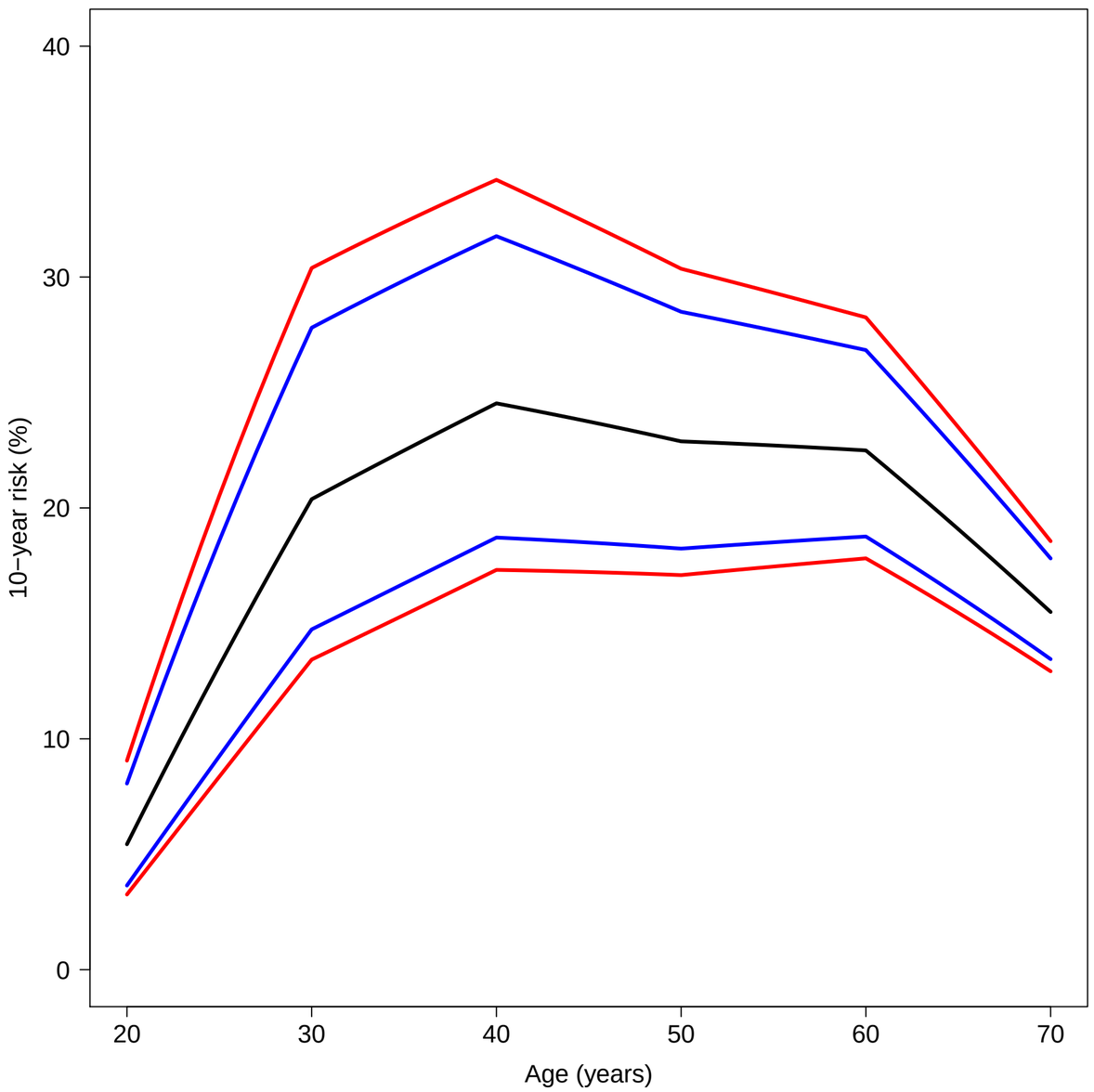
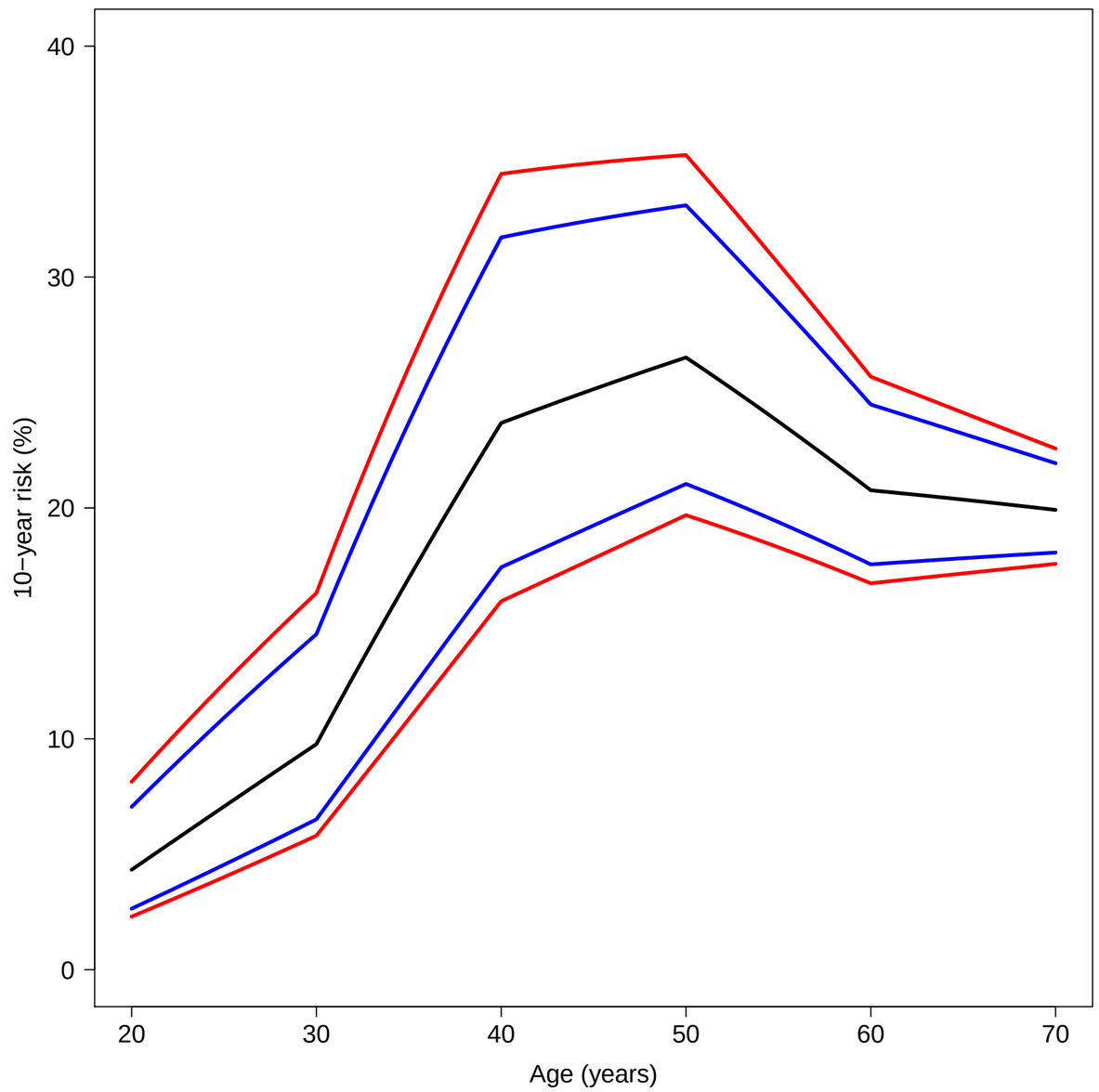
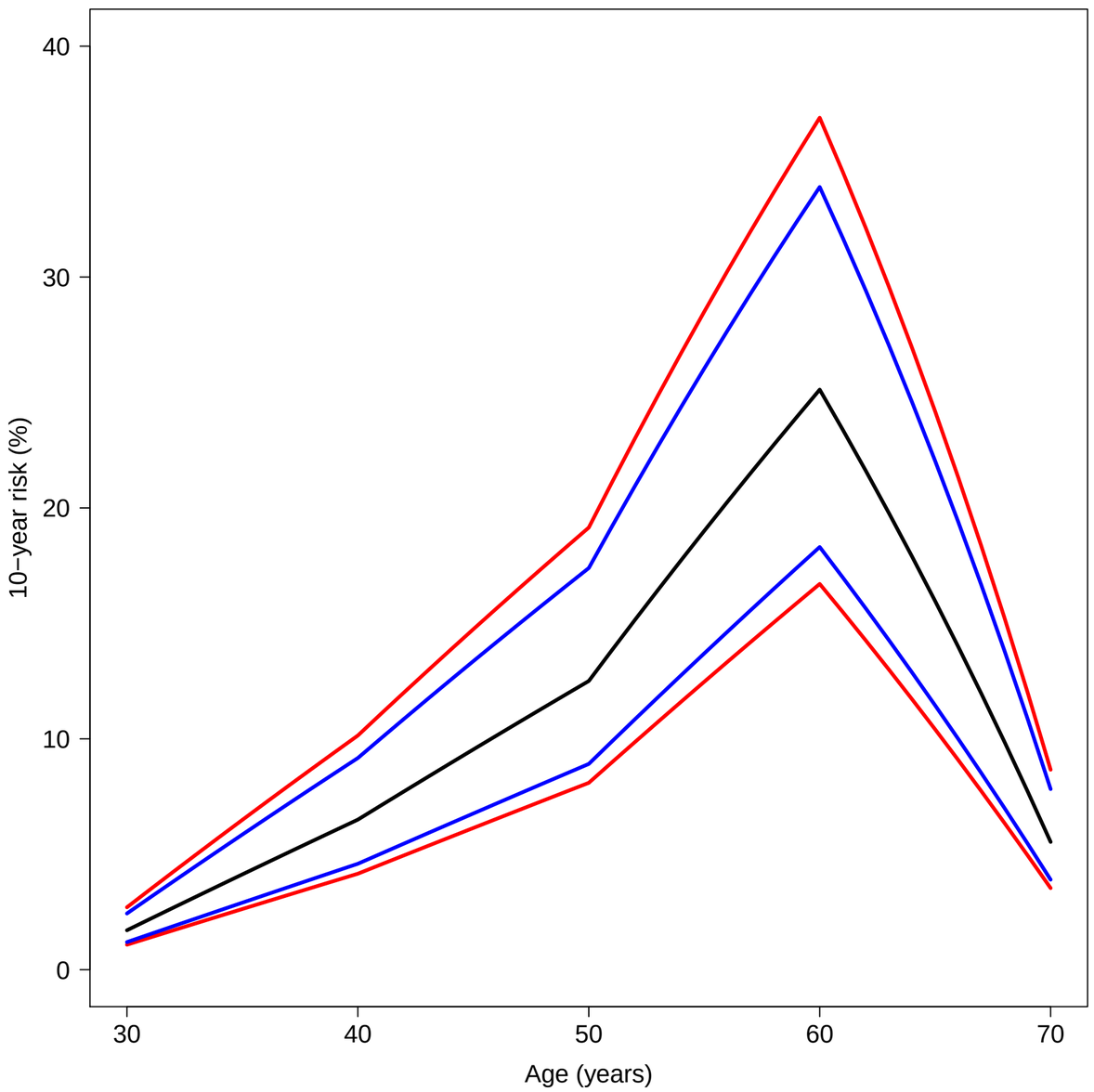


Figure S4


(A) BRCA1 carriers: ER−negative PRS
10−year risk (%)
0
10
20
30
40
20
30
40
50
60
70
Age (years)


(B) BRCA2 carriers: Overall PRS
10−year risk (%)
0
10
20
30
40
20
30
40
50
60
70
Age (years)


(C) BRCA1 carriers: HGS PRS
10−year risk (%)
0
10
20
30
40
30
40
50
60
70
Age (years)

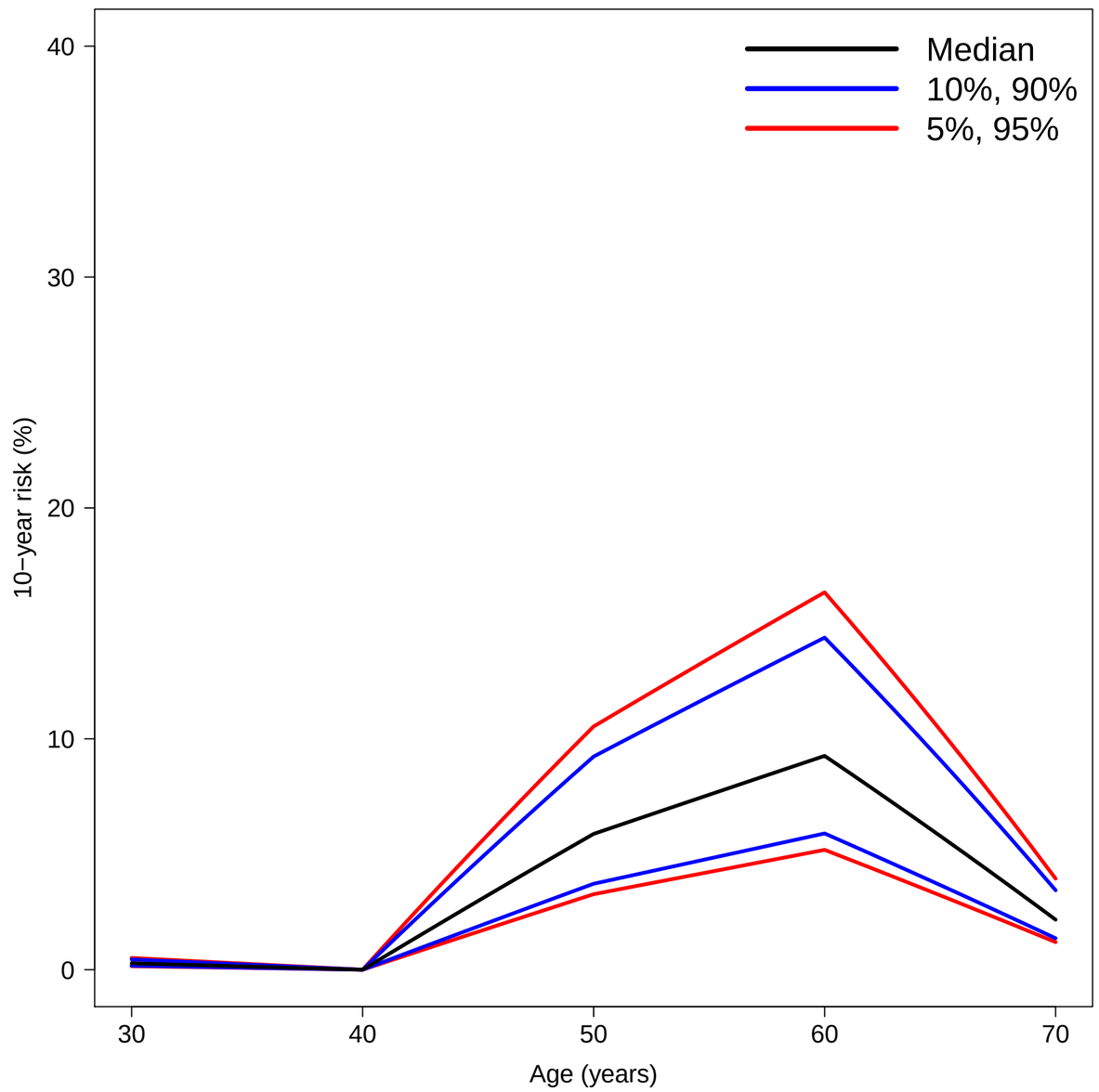

(D) BRCA2 carriers: HGS PRS
10−year risk (%)
0
10
20
30
40
30
40
50
60
70
Age (years)
Median
10%, 90%
5%, 95%

Figure S5

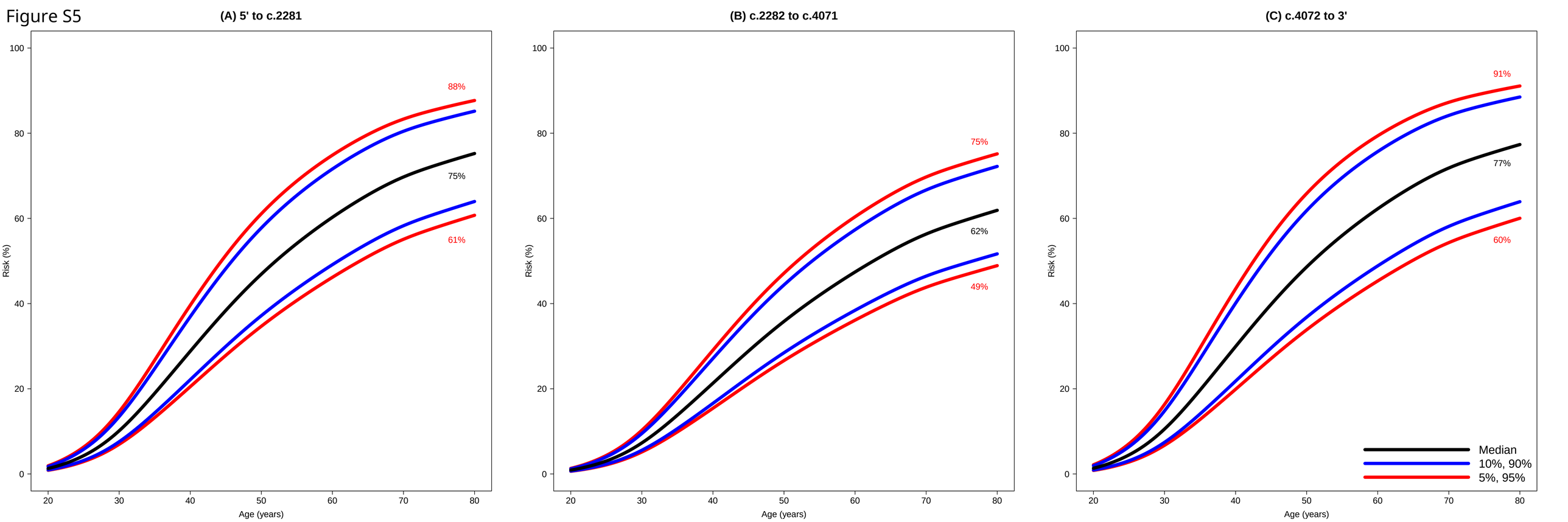

(A) 5' to c.2281
(B) c.2282 to c.4071
(C) c.4072 to 3'
Risk (%)
Age (years)
88%
75%
61%
75%
62%
49%
91%
77%
60%
Median
10%, 90%
5%, 95%

Figure S6

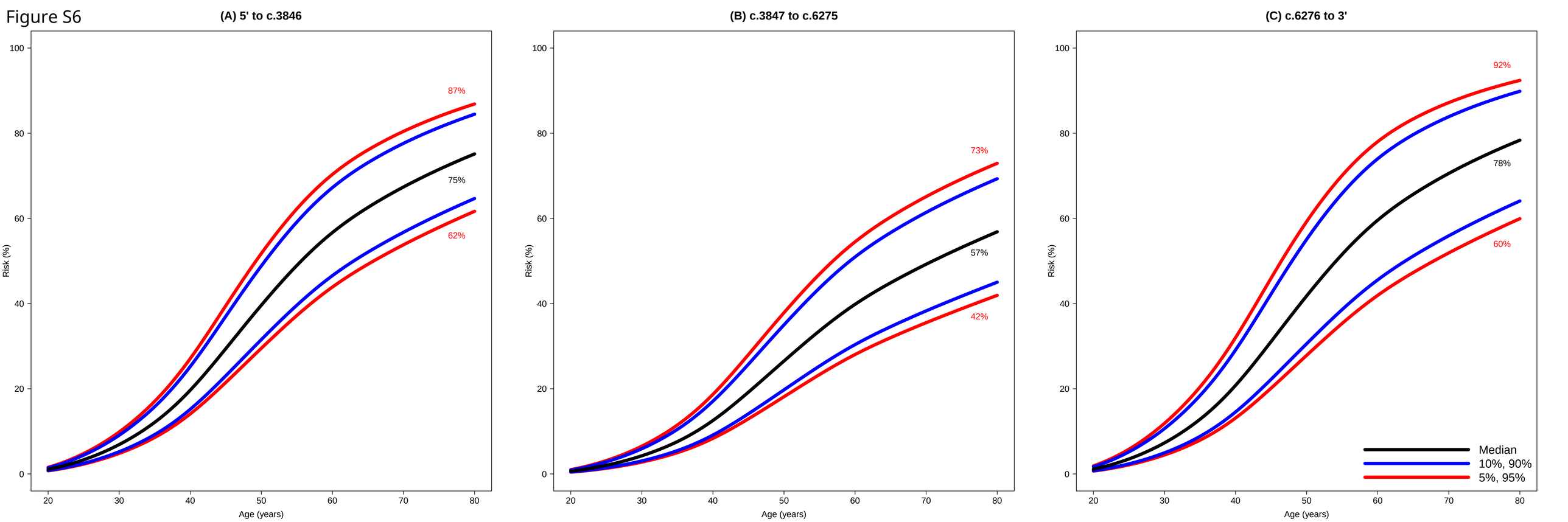

(A) 5' to c.3846
(B) c.3847 to c.6275
(C) c.6276 to 3'
Risk (%)
Age (years)
87%
75%
62%
73%
57%
42%
92%
78%
60%
Median
10%, 90%
5%, 95%

Figure S7

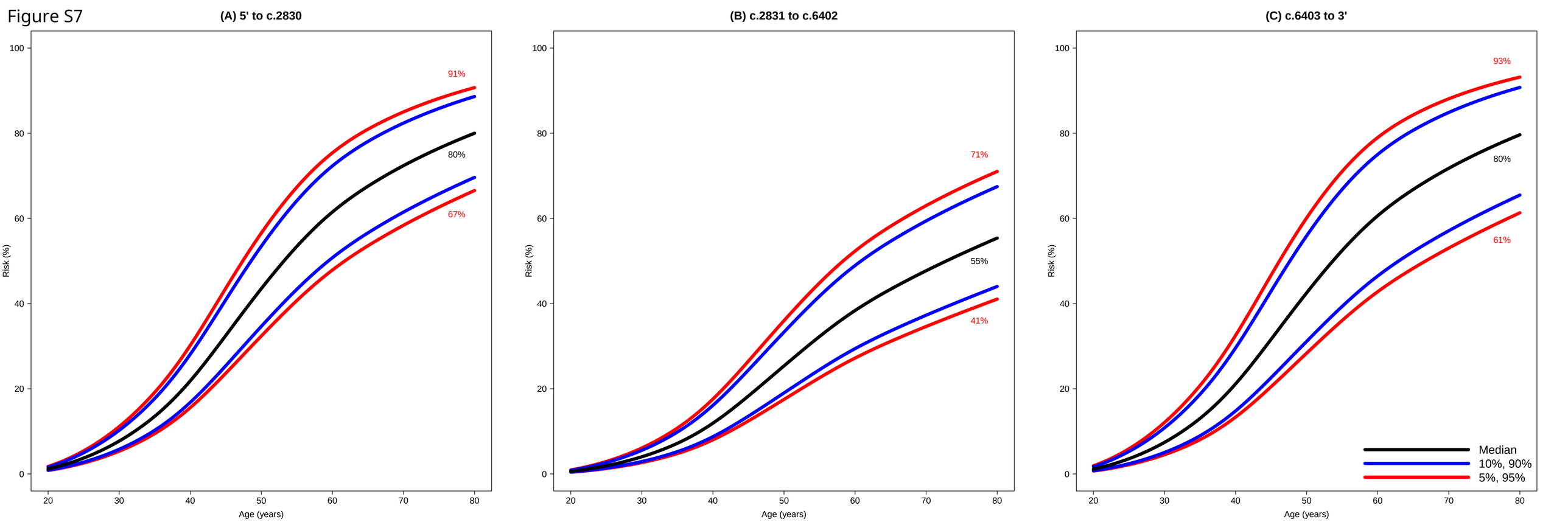

(A) 5' to c.2830
(B) c.2831 to c.6402
(C) c.6403 to 3'
Risk (%)
Age (years)
91%
80%
67%
71%
55%
41%
93%
80%
61%
Median
10%, 90%
5%, 95%

Figure S8

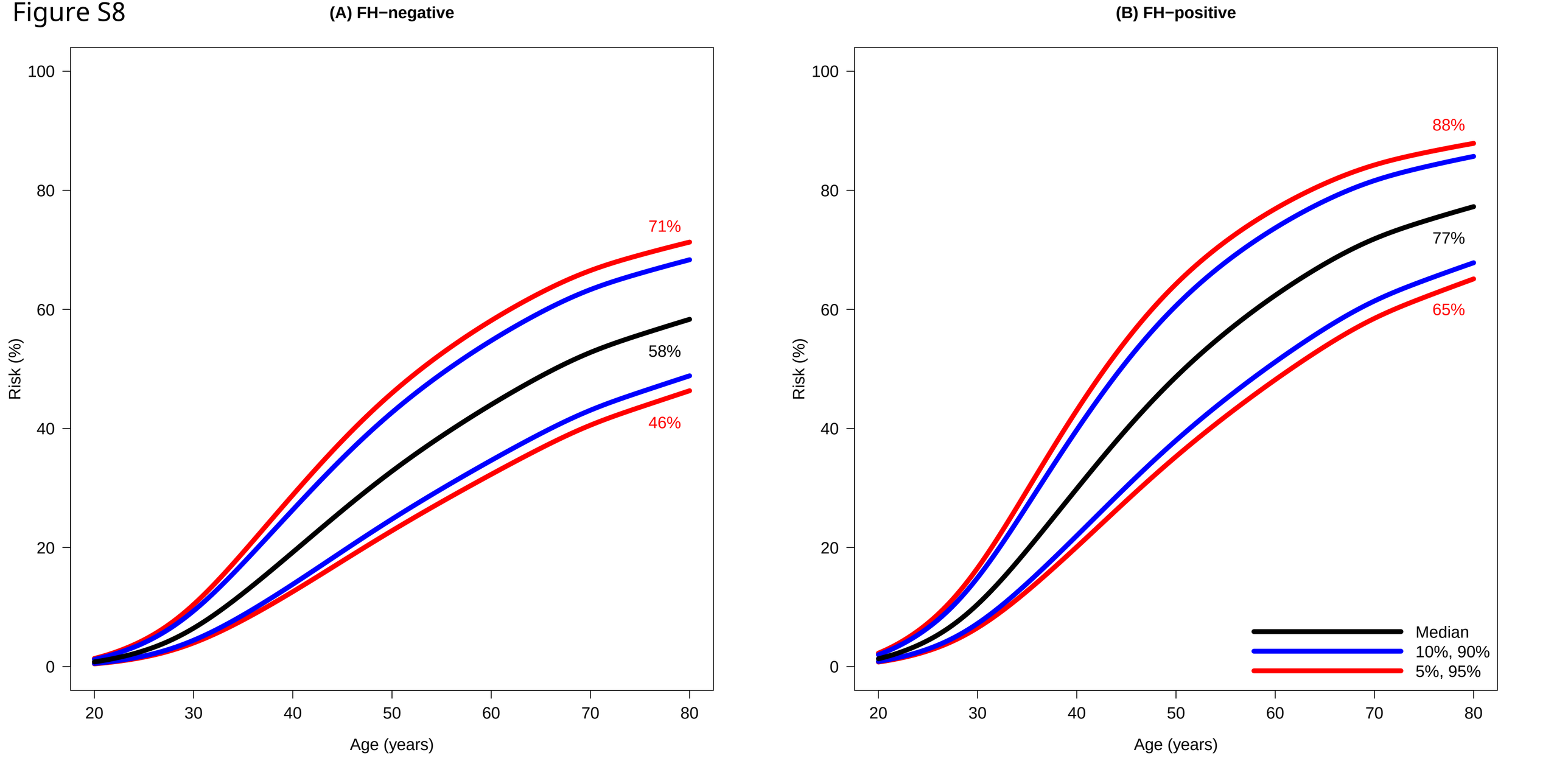
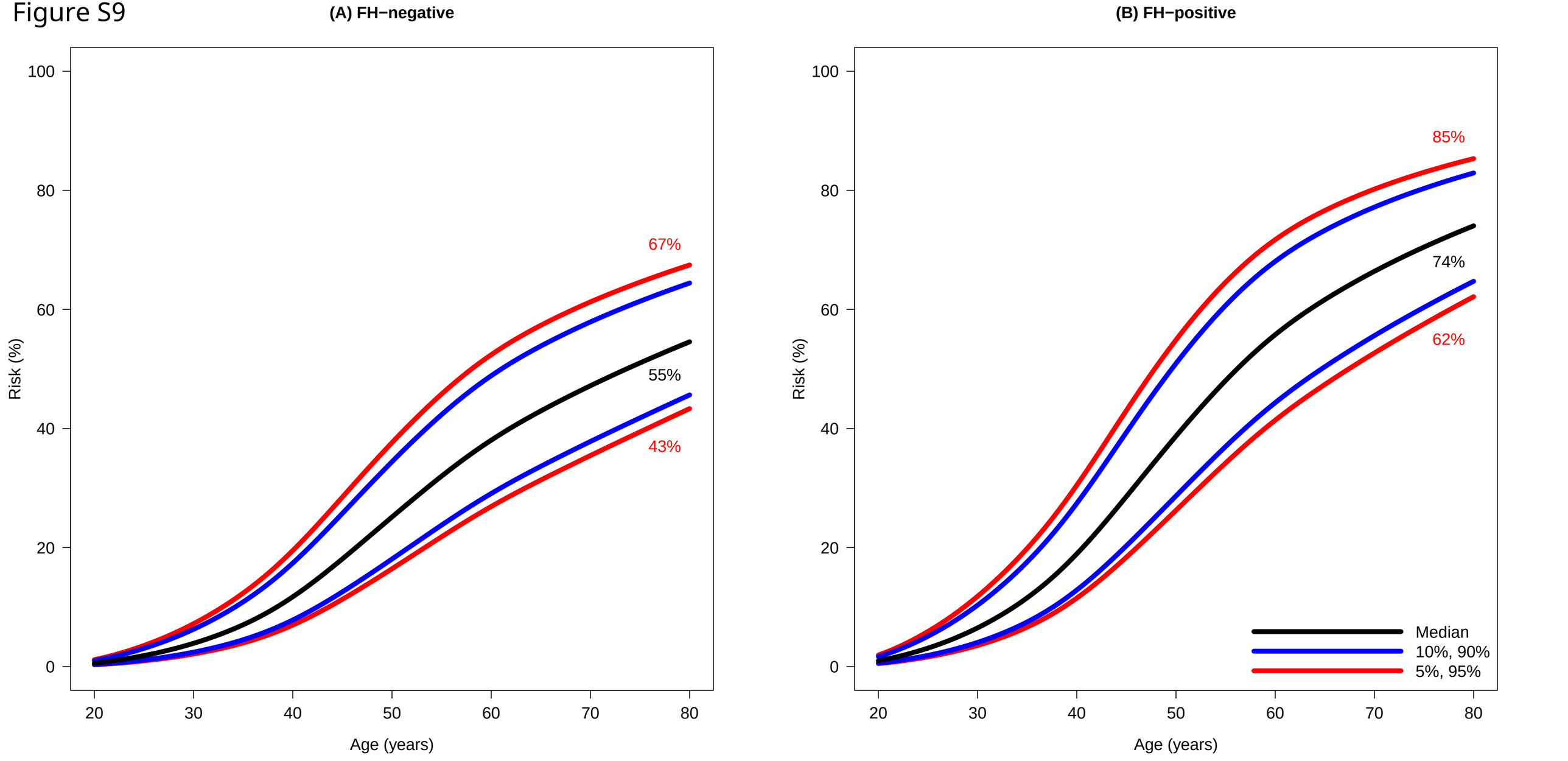

(A) FH−negative
(B) FH−positive
Risk (%)
Age (years)
0
20
40
60
80
100
20
30
40
50
60
70
80
71%
58%
46%
88%
77%
65%
Median
10%, 90%
5%, 95%

Figure S9


(A) FH−negative
(B) FH−positive
Risk (%)
Age (years)
0
20
40
60
80
100
20
30
40
50
60
70
80
67%
55%
43%
85%
74%
62%
Median
10%, 90%
5%, 95%